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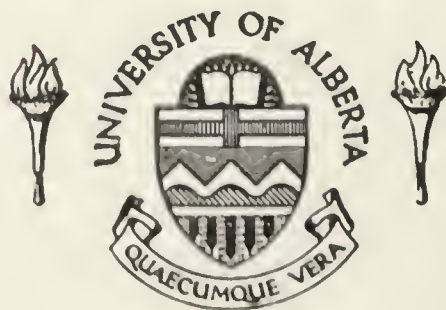
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THE ALKALOIDS OF LYCOPODIUM CLAVATUM var. MEGASTACHYON.

by

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A THESIS

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### ABSTRACT

The alkaloids of Lycopodium clavatum var. megastachyon have been examined. The major component, lycopodine, and two hitherto unreported alkaloids which we named lycoclavine and acetyllycoclavine have been studied in some detail.

The oxidation of lycopodine with potassium permanganate in neutral and acidic solution is reported, the oxidation in acidic solution giving rise to an N-formyl acid, formed by cleavage in the so-called  $\alpha$ -ring, the neutral oxidation leading to a lactam.

The reduction of lycopodine and of the above mentioned lactam with metal hydrides and with dissolving metal gave epimeric alcohols whose reactions led to the elucidation of the stereochemistry at C-4 in lycopodine.

Oxidation of the axial hydroxy lactam with lead tetraacetate gave rise to an ether which was used to prove the stereochemistry at C-15 in the alkaloid as well as to suggest a route to various dioxygenated naturally occurring compounds.

The 6-bromolycopodines have been studied and the Lycopodium lucidulum alkaloid L.20 prepared from these compounds. On the basis of some of the rotatory dispersion data presented it is suggested that positively charged nitrogen has a negative specific rotativity.

The constitution and stereochemistry of lycoclavine and acetyllycoclavine has been determined. The nuclear magnetic resonance spectra of these and related compounds are discussed in terms of the conformation of ring B in these alkaloids. The preparation of lycoclavine from lycopodine is described.

The mass spectra of several Lycopodium alkaloids are discussed and a tentative proposal is made for the structure of one of the minor alkaloids isolated during this investigation.



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## INTRODUCTION.

In 1881 Bødker pointed out (1) that Lycopodium complanatum L., a representative of the vascular cryptogams, contained an alkaloid, which he called lycopodine.

Little interest was shown in the alkaloidal content of the Lycopodiaceae for almost half a century, when the isolation work undertaken by Achmatowicz and Uzieble (2) and, notably, by Manske and Marion (3-12) led to a widespread interest in the plant family. At the time of writing (February 1963) a total of at least seventy-five alkaloids have been reported from eighteen different Lycopodium species.

TABLE I lists these species and their known alkaloidal content. In each case the name or names assigned to the alkaloid are reported, together with the molecular formula, the melting point of the free base or one of its salts and references to the isolation procedure. In cases where an alkaloid has been reported from more than one species the melting point is only recorded the first time. Subsequently reference is made in that column to other sources of the alkaloid.



TABLE I

THE ALKALOIDS OF THE LYCOPODIACEAE

(a) Lycopodium annotinum L.

NAME(S)	MOL. FORMULA	M. P.	REFERENCES
Nicotine	$C_{10}H_{14}N$	Dipicrate $226^{\circ}$	28
Unnamed	$C_{10}H_{19-21}ON$	B. $CH_3I$ $290^{\circ}$	18
Base VIII	$C_{16}H_{21}O_3N$	B. $CH_3I$ $216^{\circ}$	28
Annotine (L.11)	$C_{16}H_{21}O_3N$	$175^{\circ}$	4,17,18
Annotinine (L.7)	$C_{16}H_{21}O_3N$	$232^{\circ}$	4,18
Lycodine	$C_{16}H_{22}N_2$	$118-119^{\circ}$	19,20
L.29 (Base VI)	$C_{16}H_{23}O_2N$	B. $HClO_4$ $274^{\circ}$	12,28
Acrifoline (L.27)	$C_{16}H_{23}O_2N$	$97^{\circ}$	18,28
Unnamed	$C_{16}H_{25}ON$	B. $CH_3I$ $261^{\circ}$	18
Lycopodine	$C_{16}H_{25}ON$	$116^{\circ}$	4,16,18
Isolycopodine (L.13?)	$C_{16}H_{25}ON$	$136^{\circ}$	17,28
L.9	$C_{16}H_{25}O_2N$	$122^{\circ}$	4
Lycofoline	$C_{16}H_{25}O_2N$	$144-145^{\circ}$	33
Annofoline	$C_{16}H_{25}O_2N$	$156-157^{\circ}$	22,33
Lycodoline (L.8,L.30)	$C_{16}H_{25}O_2N$	$180^{\circ}$	4
L.10	$C_{16}H_{27}ON$	B. $HClO_4$ $223^{\circ}$	4
$\beta$ -Obscurine	$C_{17}H_{24}ON_2$	$317-318^{\circ}$	3,23
Base IX	$C_{17}H_{25}O_2N$	B. $CH_3I$ $324^{\circ}$	28
Base X	$C_{17}H_{25}O_3N$	B. $CH_3I$ $315^{\circ}$	28
A.2	$C_{17}H_{25}O_3N$	$123^{\circ}$	27,35
Annopodine	$C_{17}H_{25}O_3N$	$212^{\circ}$	27
$\alpha$ -Obscurine	$C_{17}H_{26}ON_2$	$282-283^{\circ}$	3,23
L.28 (Base V)	$C_{17}H_{27}O_2N$	B. $HClO_4$ $211^{\circ}$	28
Base XI	$C_{18}H_{25}O_3N$	B. $CH_3I$ $272^{\circ}$	28



Lycopodium annotinum L. (continued)

O-Acetyl acrifoline (L.12)	$C_{18}H_{25}O_3N$	119°	4,14
$\beta$ -Lofoline (Fawcettiine)	$C_{18}H_{29}O_3N$	166-167°	29,33
$\alpha$ -Lofoline (Lofoline)	$C_{18}H_{29}O_3N$	211-212°	33
L.31 (Base VII)	$C_{20}H_{29}O_4N$	B.HClO <sub>4</sub> 217°	28
Annotoxine (L.11+L.27)	$C_{32}H_{44}O_5N_2$	197°	18

(b) Lycopodium annotinum var. acrifolium Fern.

Annotinine (L.7)	$C_{16}H_{21}O_3N$	a	12
L.29 (Base VI)	$C_{16}H_{23}O_2N$	a	12
Acrifoline (L.27)	$C_{16}H_{23}O_2N$	a-d-p	12
Lycopodine	$C_{16}H_{25}ON$	a-d-e-f-g-h i-k-l-m-p-q-s	12
Lycodoline (L.8,L.30)	$C_{16}H_{25}O_2N$	a-d-i-j-k-p-s	12
L.28 (Base V)	$C_{17}H_{27}O_2N$	a	12
L. 31 (Base VI)	$C_{20}H_{29}O_4N$	a	12

(c) Lycopodium cernuum L.

Nicotine	$C_{10}H_{14}N_2$	a-d-g-k-l-m-q	10
Cernuine (L.32)	$C_{16}H_{26}ON_2$	106°	10,34
Lycocernuine (L.33)	$C_{16}H_{26}O_2N_2$	225°	10,34

(d) Lycopodium clavatum L.

Nicotine	$C_{10}H_{14}N_2$	a-c-g-k-l-m-q	10
L.19	?	231°	7
L.18	$C_{11}H_{19}ON$	Picrate 195°	7
Annotine (L.11)	$C_{16}H_{21}O_3N$	a-b	4,18
Acrifoline (L.27)	$C_{16}H_{23}O_2N$	a-b	18
Lycodine	$C_{16}H_{22}N_2$	a	26
De-N-methyl $\alpha$ -obscurine	$C_{16}H_{24}ON_2$	268-272°	26
Lycopodine	$C_{16}H_{25}ON$	a-b-e-f-g-h-i k-l-m-p-q-s	7,18,*

\*see experimental section this dissertation







Lycopodium clavatum L. (continued)

Isolycopodine (L.13?)	$C_{16}H_{25}ON$	a-k-l-m-q	7
Lycodoline (L.8,L.30)	$C_{16}H_{25}O_2N$	a-b-i-j-k-p-s	26
Flabelliformine (Clavatine?)	$C_{16}H_{25}O_2N$	212°	2,*
Clavolonine (L.34)	$C_{16}H_{25}O_2N$	241°	36,*
Dihydrolycopodine (L.1, Complanatine)	$C_{16}H_{27}ON$	168°	*
α-Obscurine	$C_{17}H_{26}ON_2$	a	26
Clavatoxine	$C_{17}H_{27}O_2N$	185-186°	2
Lycoclavine	$C_{18}H_{29}O_3N$	212-213°	*
Annotoxine (L.11,L.27)	$C_{32}H_{44}O_5N_2$	a	18
"Complex" (L.1-Flabelliformine)	$C_{32}H_{52}O_3N_2$	208°	*

(e) Lycopodium clavatum (Jamaica)

Lycopodine	$C_{16}H_{25}ON$	a-b-d-f-g-h i-k-l-m-p-q-s	32
Clavoloinine (L.34)	$C_{16}H_{25}O_2N$	d	32
Dihydrolycopodine (L.1,Complanatine)	$C_{16}H_{27}ON$	d-f-g	32
Deacetylfawcettiine	$C_{16}H_{27}O_2N$	203-204°	32
Fawcettiine (β-Lofoline)	$C_{18}H_{29}O_3N$	a	32
Fawcettimine		B.CH <sub>3</sub> I 241°	32

(f) Lycopodium clavatum var megastachyon

Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-g-h i-k-l-m-p-q-s	*
Flabelliformine (Clavatine?)	$C_{16}H_{25}O_2N$	d-g-q-	*
Diol I	$C_{16}H_{25}O_2N$	261-263°	*
Dihydrolycopodine (L.1, Complanatine)	$C_{16}H_{27}ON$	d-e-g	*
Clavolonine (L.34)	$C_{16}H_{27}O_2N$	d-e	*

\*see experimental section - this dissertation



Lycopodium clavatum var megastachyon (continued)

O-Acetyldihydrolycopodine (L.2)	$C_{18}H_{29}O_2N$	97°	*
Lycoclavine	$C_{18}H_{29}O_3N$	d	*
O-Acetyllycoclavine	$C_{20}H_{31}O_4N$	144-145°	*
"Complex" (L.1:Flabelliformine)	$C_{32}H_{52}O_3N$	d-g	*

(g) Lycopodium complanatum L. (Lycopodium flabelliforme)

Nicotine	$C_{10}H_{14}N_2$	a-c-d-k-l-m-q	3
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-h-i k-l-m-p-q-s	3,5
Flabelliformine (Clavatine?)	$C_{16}H_{25}O_2N$	d-f	21
L.4	$C_{16}H_{27}N$	B.HClO <sub>4</sub> 225°	3
Dihydrolycopodine (L.1, Complanatine)	$C_{16}H_{27}ON$	d-e-f	3
β-Obscurine	$C_{17}H_{24}ON_2$	a	3
α-Obscurine	$C_{17}H_{26}ON_2$	a-d	3
L.5	$C_{18}H_{28}O_2N_2$	B.HClO <sub>4</sub> 282°	3
O-Acetyldihydrolycopodine (L.2)	$C_{18}H_{29}O_2N$	f	3
L.3	$C_{18}H_{31}O_2N$	B.HClO 246°	3
"Complex" (L.1:Flabelliformine)	$C_{32}H_{52}O_3N$	d-f	*

(h) Lycopodium densum L.

L.35	$C_{14}H_{21}ON$	133°	11
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-k i-l-m-p-q-s	11
Clavolonine (L.34)	$C_{16}H_{25}O_2N$	d-e-f	11

(i) Lycopodium prostratum Harper

Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h k-l-m-p-q-s	97
Lycodoline (L.8,L.30)	$C_{16}H_{25}O_2N$	a-b-d-j-k-p-s	97

\*see experimental section - this dissertation



Lycopodium prostratum Harper (continued)

Prostratine	$C_{16}H_{25}O_3N$	179-180°	97
Base "253"	$C_{23}H_{27-29}O_4N$	253°	97
(j) <u>Lycopodium fawcettii</u> L.			
Fawcettidine (Base F)	$C_{16}H_{23}ON$	Picrate 222°	30
Lycodoline (L.8, L.30)	$C_{16}H_{25}O_2N$	a-b-i-k-p-s	30
Lycofoline	$C_{16}H_{25}O_2N$	a	29
Base A (Fawcettimine)	$C_{16}H_{27}O_2N$	e	30
De-acetylfawcettiine	$C_{16}H_{27}O_2N$	e	30
Base E	$C_{17}H_{25}O_2N$	B.HClO <sub>4</sub> 267°	30
Base M (5-Acetyllycofoline)	$C_{18}H_{27}O_2N$	B.HClO <sub>4</sub> 280-282°	29
Base G	$C_{18}H_{27}O_3N$	B.HClO <sub>4</sub> 200°	30
Fawcettiine (β-Lofoline)	$C_{18}H_{29}O_3N$	a-e	29, 30
Base O	$C_{20}H_{21}O_5N$	181-182°	29
Diacetyllycofoline (Base N)	$C_{20}H_{29}O_4N$	140°	29
Acetylfawcettiine (Base K)	$C_{20}H_{31}O_4N$	116°	29

(k) Lycopodium lucidulum Michx.

Nicotine	$C_{10}H_{14}N_2$	a-c-d-g-l-m-q	8
L.21	$C_{13}H_{21}ON$	107°	8
L.24	$C_{16}H_{25}ON$	B.HClO <sub>4</sub> 278°	8
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-h-i g-l-m-p-q-s	8, 26
L.13 (Isolycopodine?)	$C_{16}H_{25}ON$	a-d-l-m-q	8
L.25	$C_{16}H_{25}O_2N$	B.HClO <sub>4</sub> 297°	8
L.23 (ψ-Selagine?)	$C_{16}H_{25}O_2N$	161-162°	8
L.8 (L.30, Lycodoline)	$C_{16}H_{25}O_2N$	a-b-d-i-j-p-s	26
L.22	$C_{16}H_{27}ON$	108°	8
L.20	$C_{16}H_{25}O_2N$	259°	8, 26

(l) Lycopodium obscurum var dendroidum

Nicotine	$C_{10}H_{14}N_2$	a-c-d-g-k-m-q	6
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Lycopodium obscurum var dendroidum (continued)

Lycodine	$C_{16}H_{22}N_2$	a-d	20
L.16	$C_{16}H_{25}ON$	B.HClO <sub>4</sub> 221°	6
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h i-k-m-p-q-s	6
L.13 (Isolycopodine)	$C_{16}H_{25}ON$	a-d-k-m-q	8
β-Obscurine	$C_{17}H_{24}ON_2$	a-g	6
α-Obscurine	$C_{17}H_{26}ON_2$	a-d-g	6
L.17	$C_{18}H_{27}O_3N$	B.HClO <sub>4</sub> 296°	6

(m) Lycopodium sabinaefolium Willd.

Nicotine	$C_{10}H_{14}N_2$	a-c-d-g-k-l-q	9
L.26	$C_{15}H_{25}ON$	171°	9
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h i-k-l-p-q-s	9
L.13 (Isolycopodine?)	$C_{16}H_{25}ON$	a-d-k-l-q	9

(n) Lycopodium saurusus Lam.

Saururine	$C_{10}H_{19}N$	B.CH <sub>3</sub> I 244°	24
Pillajanine	$C_{15}H_{24}ON_2$	64-65°	25
Sauroxine	$C_{17}H_{26}ON_2$ or $C_{16}H_{24}ON_2$	198°	24

(o) Lycopodium selago L.

Selagine	$C_{15}H_{18}ON_2$	224-226°	36
Annotine (L.11)	$C_{16}H_{21}O_3N$	a-b-d	17
Acrifoline (L.27)	$C_{16}H_{23}O_2N$	a-b-d	16
Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h i-k-l-m-q-s	16
ψ-Selagine (L.23?)	$C_{16}H_{25}O_2N$	k	16
L.8 (L.30, Lycodoline)	$C_{16}H_{25}O_2N$	a-b-d-i-j-k-s	16

(p) Lycopodium tristachyum Purch.

Nicotine	$C_{10}H_{14}N_2$	a-c-d-g-k-l-m	5
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Lycopodium tristachyum Purch. (continued)

L.14 (Anhydrodihydro-lycopodine)	$C_{16}H_{25}N$	B.HClO <sub>4</sub> 238°	5,15
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Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h i-k-l-m-p-s	5
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L.13 (Isolycopodine)	$C_{16}H_{25}ON$	a-d-k-l-m	5
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L.15	$C_{20}H_{31}O_4N?$	B.HClO <sub>4</sub> 231°	5
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(q) Lycopodium alopecuroides L.

One uncharacterized base reported			13
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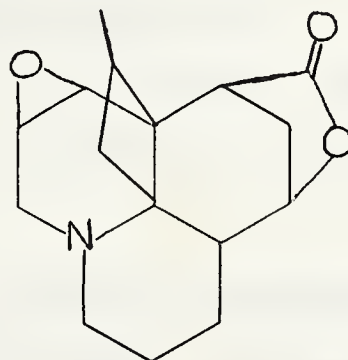
(r) Lycopodium phlegmaria L.

Lycopodine	$C_{16}H_{25}ON$	a-b-d-e-f-g-h i-k-l-m-p-q	41
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Lycodoline (L.8,L.30)	$C_{16}H_{25}O_2N$	a-b-d-i-j-k-p	41
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Several other poorly characterized bases were also isolated from this species.			41
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When this work was initiated in 1958 the only *Lycopodium* alkaloid of known structure was annotinine I. The structure of this alkaloid had been determined by Wiesner and co-workers (37) and later confirmed by an X-ray crystallographic study of annotinine bromohydrin (38).



I

Lycopodine had been the object of some study, but conclusions about the partial structure of the alkaloid were rather limited. Manske and Marion had originally suggested that the oxygen atom occurs in the form of an ether linkage (39). This conclusion



was based on the observations that lycopodine did not react with phenyl magnesium bromide and could not be reduced with Raney nickel at 200° and 2000 lbs. p.s.i.. However, it was later shown by MacLean, Manske and Marion (40) that lycopodine contains a carbonyl group. They showed that lycopodine exhibits a maximum in the infrared at  $1693\text{ cm}^{-1}$ , reacts with hydrazine to form a hydrazone, can be reduced with lithium aluminum hydride to a secondary alcohol and reacts with phenyl lithium to give a tertiary carbinol. The nitrogen atom in lycopodine appeared to be tertiary and thus it was concluded that the alkaloid is tetracyclic.

Dehydrogenation experiments suggested that lycopodine contains a reduced quinoline system (39). Attempted ring cleavage of lycopodine by the Emde or Hofmann methods was unsuccessful (39) but ring fission did occur with the von Braun method. Treatment of lycopodine with cyanogen bromide gave a mixture of two products, named  $\alpha$ - and  $\beta$ -cyanobromolycopodine (40). The  $\alpha$ -compound was converted to the corresponding cyanohydroxylycopodine, which could be oxidized without carbon loss to a cyano acid. Lycopodine must, therefore contain the grouping  $\text{>N}\cdots\text{CH}_2-$ , the  $\alpha$ -compound being formed by cleavage of the bond indicated by the broken line.

Our work on the structure of lycopodine started with little more positive evidence than that outlined above.

Subsequent relevant publications by other workers will be dealt with in the discussion section below, since their inclusion illustrating a chronological relationship to our work is more meaningful.





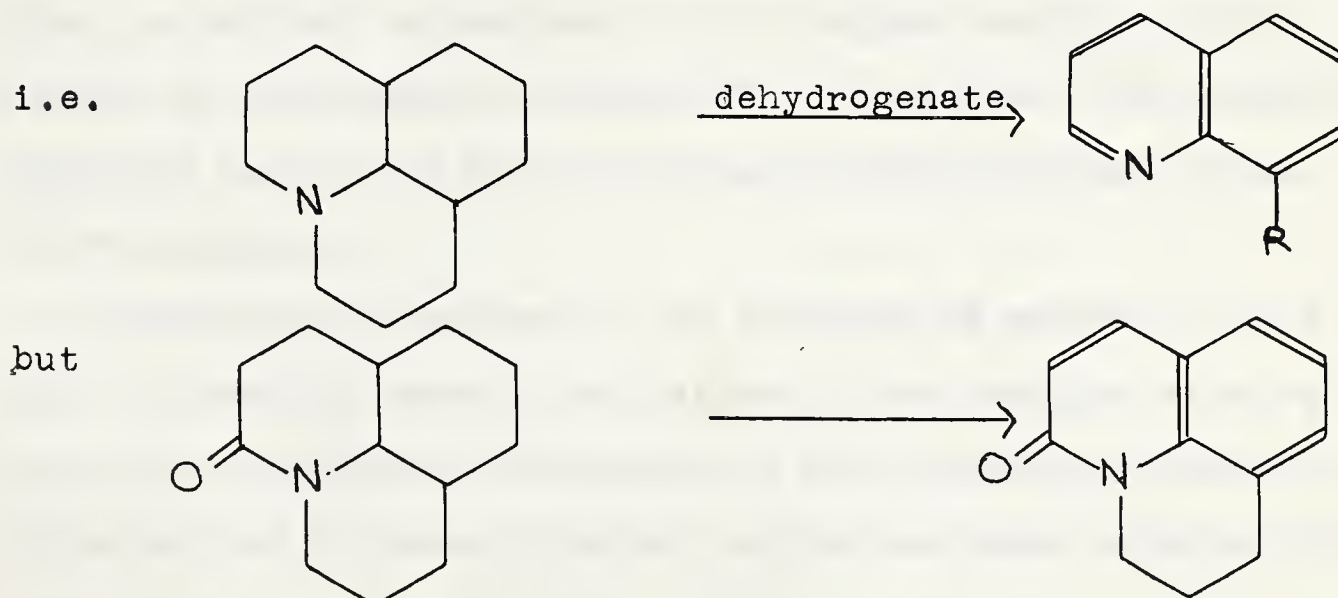


## DISCUSSION AND RESULTS.

### I. THE OXIDATION OF LYCOPODINE.

#### (a) Potassium permanganate in aqueous solution.

When this work was initiated in 1958 the constitution of lycopodine was not known. It has been shown (39) that dehydrogenation of the alkaloid with selenium yielded 7-methylquinoline, 5:7-dimethylquinoline and several unidentified bases. The fact that 7-methylquinoline was also obtained under very mild conditions, using palladium charcoal (39) suggested that the reduced quinoline nucleus was present in the lycopodine molecule. By analogy with annotinine (47) it was hoped that the julolidine nucleus, if present in lycopodine, would be retained on dehydrogenation of the lactam previously prepared from lycopodine by MacLean (48), since in the lactam series an aromatic system could be obtained without further ring opening.



The required lactam, however, had been prepared from lycopodine only in moderate yield by a several stage process (48) and a more direct route was sought.

Direct oxidation of lycopodine using potassium permanganate in aqueous oxalic acid at room temperature apparently gave the



lactam, albeit in very low yield. The major product, formed without carbon loss in 40% yield, was an acid II, m.p. 244-245°. This acid, which analyzed for  $C_{16}H_{23}O_4N$ , showed maxima in the infrared at 1712, 1655 and 1618  $cm^{-1}$  (in chloroform) and at 1740, 1715 and 1638  $cm^{-1}$  (nujol mull), together with carboxyl group absorption centered at 3000  $cm^{-1}$  in both cases.

The corresponding methyl ester III,  $C_{17}H_{25}O_4N$ , m.p. 117°, showed infrared maxima at 1742, 1720 and 1660  $cm^{-1}$  (in chloroform) and at 1732, 1710 and 1652  $cm^{-1}$  (nujol mull).

Reduction of the ester III with sodium borohydride in methanol gave the hydroxy ester IV,  $C_{17}H_{27}O_4N$ , m.p. 206°, which exhibited maxima in the infrared at 3550, 1746 and 1657  $cm^{-1}$  (in chloroform) and at 3300, 1733 and 1635  $cm^{-1}$  (nujol mull). The keto acid II was recovered unchanged after similar treatment.

The analytical and spectral data above clearly indicate that the primary oxidation product II contains a ketonic carbonyl group, a carboxyl group and a third oxygen function, which absorbs in the region characteristic of amides. The experiments described next prove that this third oxygen function is an N-formyl group.

Hydrolysis of either III or IV using 3N sulphuric acid at 100° followed by steam distillation of the reaction mixture gave an acidic distillate. Titration of the distillate from the hydrolysis of II using standard sodium hydroxide solution gave a value corresponding to 49% of the theoretical mono-acid (see Experimental section). Reduction of the acidic distillate with magnesium-hydrochloric acid (49) yielded a dilute solution of formaldehyde. The presence of the latter was proved in two ways.





In one experiment the chromotropic acid complex was formed (50). This was identified by its visible spectrum, the three bands reported earlier (51) at 380, 480 and 570  $m\mu$  all being present. The maximum at 480  $m\mu$  had only half the intensity of the other peaks as reported earlier (51). The spectra were identical to that exhibited by the chromotropic acid complex of authentic formaldehyde.

In a second experiment the reduced solution from the hydrolysis of the hydroxy ester obtained by the procedure outlined above was treated with dimedone solution (52). The crystalline product, which melted at 184-187°, had an infrared spectrum identical to that of the dimedone derivative of authentic formaldehyde (m.p. 192°). The mixed melting point on admixture of the two samples was 185-188°.

The amino acid VI, formed in the hydrolysis of III, was obtained from the acidic reaction mixture by continuous extraction with ether. The pale yellow oil, which showed infrared maxima at 1720 and 1625  $cm^{-1}$  (in chloroform) but no absorption at 1660  $cm^{-1}$ , could not be purified either as the amino acid or as the corresponding methyl ester. Attempted ring closure to the corresponding lactam led only to intractable gums.

The hydroxy amino acid VII from the hydrolysis of IV was extracted from the reaction mixture as an intractable dark oil.

Mild hydrolysis of the N-formyl hydroxy ester IV using 2% sodium hydroxide in 50% ethanol at room temperature gave the hydroxy acid V,  $C_{16}H_{25}O_4N$ , m.p. 211°, in good yield. The hydroxy acid V showed infrared maxima at 3675, 3500 and 1675  $cm^{-1}$  (in chloroform) and at 3450, 1698 and 1600  $cm^{-1}$  (nujol mull) together



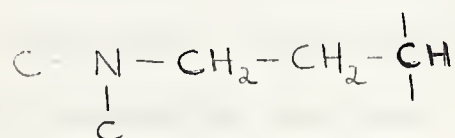


with carboxyl -OH absorption centered at  $3000\text{ cm}^{-1}$  in both cases.

Three conclusions can be drawn from the sequence of reactions described above.

First, in lycopodine, the nitrogen atom must be attached in the direction of oxidative attack to a  $-\text{CH}_2-\text{CH}_2-$  group.

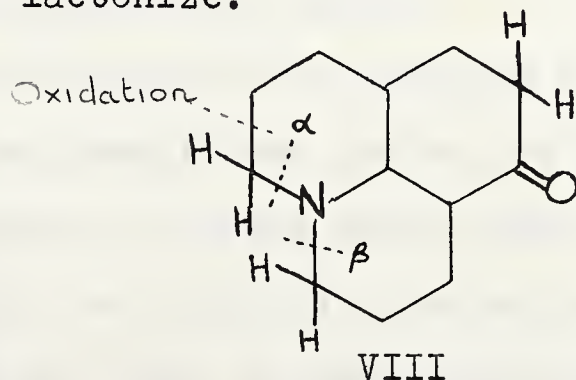
Secondly, the ease of hydrolysis of the ester IV to the acid V suggests that the ester group is not tertiary. The partial structure of lycopodine could thus be extended to



The N-formyl acid is produced by cleavage of the bond joining the two methylene groups.

Finally, the hydroxy acid V was obtained as the free acid and not as the corresponding lactone. In fact V was recovered unchanged after refluxing for twelve hours in dry benzene containing p-toluenesulphonic acid.

At this time MacLean reported evidence (48) for the partial structure VIII for lycopodine. From this structure, the evidence for which is described below, it appeared that oxidation to the N-formyl acid II had occurred with cleavage in the  $\alpha$  ring, since  $\beta$ -cleavage would have led to a  $\gamma$ -hydroxy acid which might be expected to lactonize.



MacLean, Manske and Marion had previously (40) reported the



preparation of  $\alpha$ - and  $\beta$ -cyanobromolycopodine (IX and X) by the action of cyanogen bromide on lycopodine. MacLean's evidence for the part structure VIII was as follows. The  $\beta$ -compound X was converted to the corresponding hydroxy acid XI which readily formed the lactone XII. The corresponding  $\alpha$ -compound would not lactonize (40). This indicates that the N-formyl acid II is formed by cleavage of the  $\alpha$ -ring, since the hydroxy acid V would not lactonize. The infrared spectrum of the lactone XII, which showed a maximum at  $1743\text{ cm}^{-1}$  indicated that XII contains a five or more likely, a six membered lactone.

Both  $\alpha$ -cyanobromolycopodine IX and the  $\beta$ -isomer X were converted to the corresponding amino esters which gave rise to the lactams XIII and XIV respectively (44,48). The  $\alpha$ - and  $\beta$ -lactams showed infrared maxima at  $1630$  and  $1626\text{ cm}^{-1}$  respectively, suggesting that they were both  $\delta$ -lactams. Both lactams gave dihydrolycopodine on reduction with lithium aluminum hydride, proving that no skeletal rearrangement had occurred during either reaction sequence (44,48), and therefore showing that, in lycopodine, the nitrogen atom is at the junction of two six membered rings. The infrared spectrum of lycopodine which shows a maximum at  $1698\text{ cm}^{-1}$  (in chloroform) indicates that the carbonyl ring is six membered or larger.

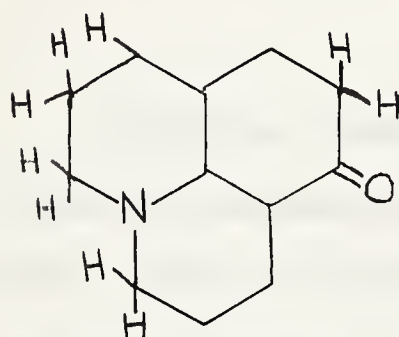
$\alpha$ -Cyanolycopodine (IX; replace Br by H) was converted to the corresponding benzylidene derivative XV (42) showing that the carbonyl group is flanked on at least one side by a methylene group.

Finally, the fact that lycopodine contains a reduced quinoline system (39) and that the hexahydrojulolidine nucleus is present in annotinine (37,47) suggested that the partial structure of

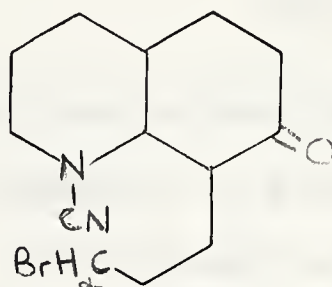


lycopodine can, in fact, be represented by structure VIII. The reactions described above in the N-formyl series allow an extension of the partial structure to XVI.

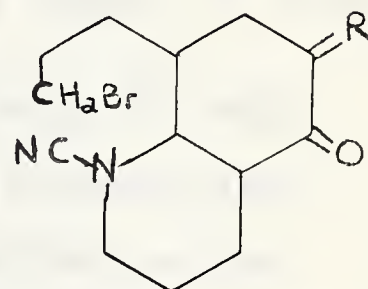
The reactions described above can thus be illustrated by the following partial structures.



XVI

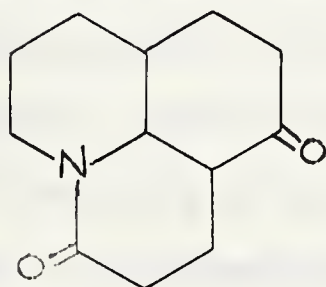


X

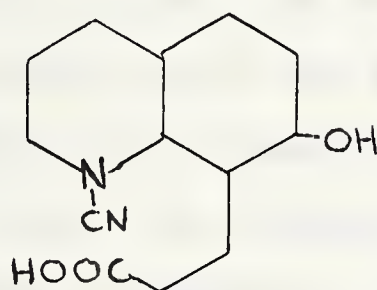


IX, R = H<sub>2</sub>

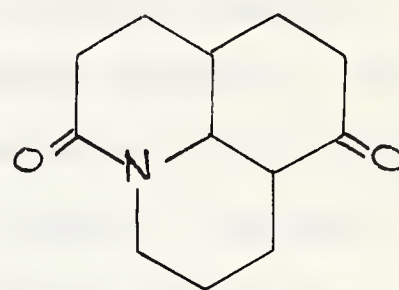
XV, R = CH $\phi$



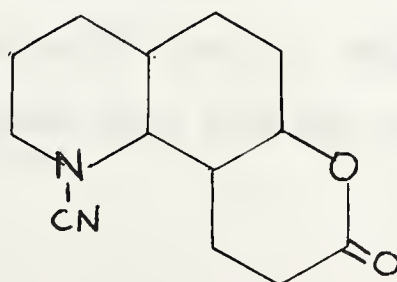
XIV



XI



XIII

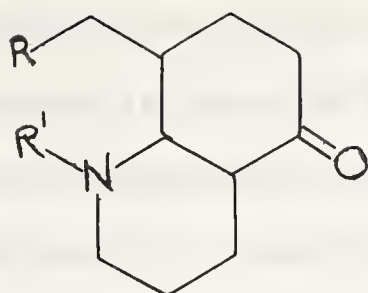


XII

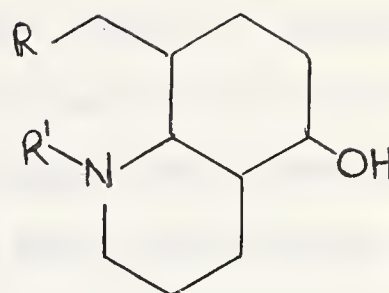








II: R = COOH, R' = CHO  
 III: R = COOCH<sub>3</sub>, R' = CHO



IV: R = COOCH<sub>3</sub>, R' = CHO  
 V: R = COOH, R' = CHO  
 VII: R = COOH, R' = H  
 XVII: R = CH<sub>2</sub>OH, R' = CH<sub>3</sub>

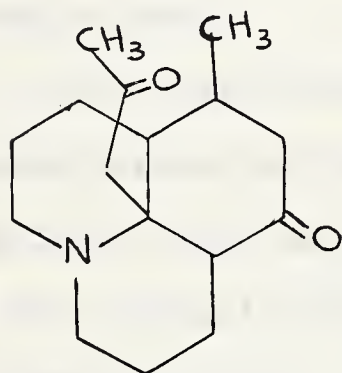
Complete reduction of the N-formyl keto ester III with lithium aluminum hydride appeared to give the N-methyl diol XVII. The oily product, which showed no absorption in the infrared between 1600 and 1800 cm<sup>-1</sup>, was unstable and was not investigated in detail.

At this point our attention turned to the Nuclear Magnetic Resonance (NMR) spectrum of lycopodine. This spectrum showed a doublet at 9.14 $\tau$  ( $J = 5.0$  c.p.s.) the area under which was approximately 3/25 of the area under the entire spectrum. This doublet, which is the only strong absorption above 8.6 $\tau$ , indicates the presence of one, and only one, C-methyl group. The fact that this three proton signal appears as a doublet indicates that the grouping is, in fact,  $\text{>CH-CH}_3$ . Kuhn-Roth C-methyl determination also indicated the presence of a single methyl group.

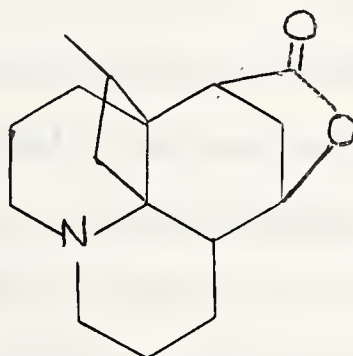
On the basis of this information it was now possible to extend the partial structure XVI and to suggest possible complete structures which would agree with all the chemical and physical data at hand.



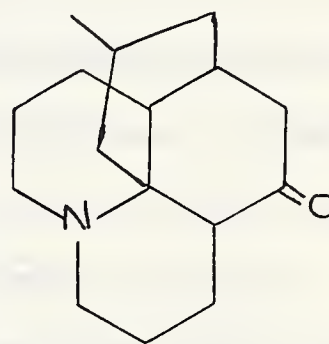
Without a detailed consideration of the biogenetic hypotheses involved (this will be discussed later) it appeared that a reasonable intermediate which could lead both to the annotinine skeleton XIX and to compounds which would have all the properties of lycopodine discussed to this point would be the intermediate XVIII.



XVIII



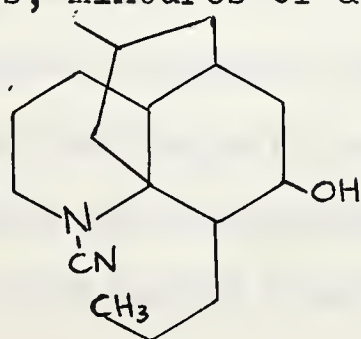
XIX



XX

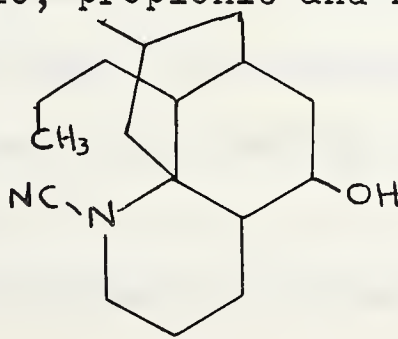
Lycopodine contains only one C-methyl group. Ring closure of the intermediate XVIII would then of necessity involve either the cyclohexanone methyl group or the open chain methyl group. The first possibility would give the skeleton XX. The second type of cyclization could lead to several different structures.

At this point (March 1960) MacLean showed (44,53) that lycopodine can in fact be represented by structure XX. He found that modified Kuhn-Roth oxidation (54) of  $\alpha$ -cyanodihydrolycopodine XXI and  $\beta$ -cyanodihydrolycopodine XXII gave, in both cases, mixtures of acetic, propionic and n-butyric acids.

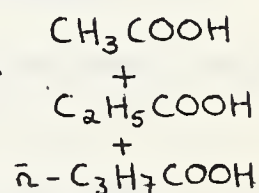


XXII

OR



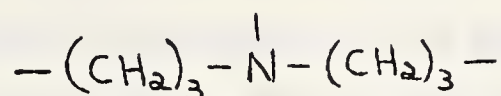
XXI





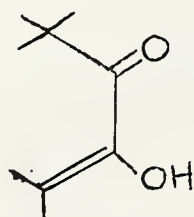


This proves that lycopodine contains the following grouping.

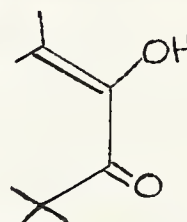


The  $\alpha$ -compound XXI gave a high proportion of n-butyric acid, suggesting that the  $\gamma$  carbon in the chain was not quaternary. This result eliminates the possibility of an annotinine skeleton. Under the same oxidation conditions lycopodine yielded only acetic acid.

The key intermediate in the structural proof was the benzylidene derivative XXIII of  $\alpha$ -cyanolycopodine. Ozonolysis of XXIII gave an enolic  $\alpha$ -diketone which had also been prepared from  $\alpha$ -cyanolycopodine by bromination followed by basic hydrolysis (42). The diketone must have at least one enolizable hydrogen and can therefore be represented by structure XXIV or XXV.



XXIV



XV

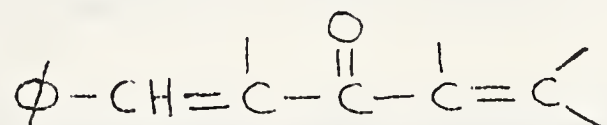
Oxidation of XXIII with selenium dioxide gave two products. The first of these which analyzed for  $\text{C}_{24}\text{H}_{30}\text{O}_2\text{N}_2$ , showed a maximum in the ultraviolet at  $280 \text{ m}\mu$  and infrared maxima at  $3560$  and  $1692 \text{ cm}^{-1}$ . The benzylidene derivative XXIII had an infrared maximum at  $1685 \text{ cm}^{-1}$ . The bathochromic shift on oxidation suggests that an axial hydroxyl group had been introduced  $\alpha$  to the carbonyl.

The second oxidation product analyzed for  $\text{C}_{24}\text{H}_{28}\text{ON}_2$  (i.e. two

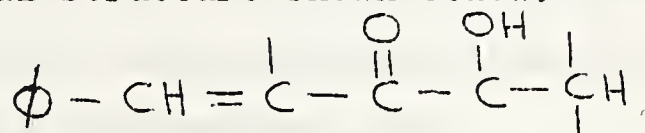




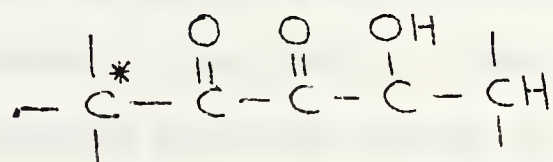
hydrogen atoms less than the starting material). This product showed an ultraviolet maximum at  $310\text{ m}\mu$  and infrared maxima at  $1677$ ,  $1626$  and  $1590\text{ cm}^{-1}$ . This suggests the following partial structure.



Both compounds gave the same product on catalytic hydrogenation, showing that no rearrangement had occurred during the oxidation. The hydroxylated oxidation product must therefore have the partial structure shown below.

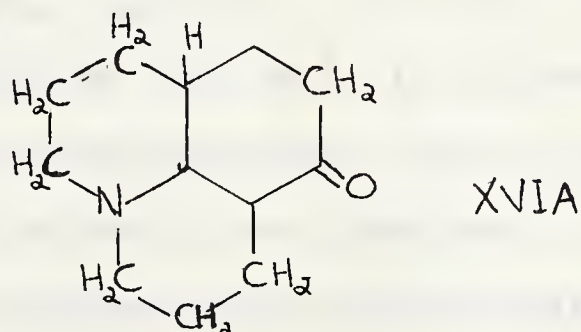


Ozonolysis of the hydroxylic compound gave a diketone which exhibited an ultraviolet maximum at  $420\text{ m}\mu$ . This compound does not, therefore, exist in the enol form and must have the partial structure



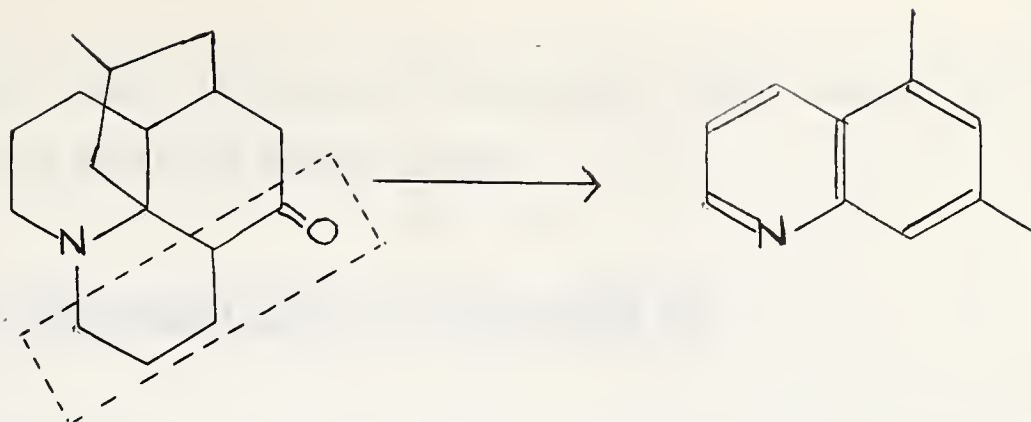
where the starred carbon is either quaternary or at a bridgehead.

From this evidence the partial structure XVI was extended to XVII.



The facile production of 7-methylquinoline and 5,7-dimethylquinoline was then used as evidence for the location of the fourth ring and the methyl group. i.e.





(b) Oxidation of Lycopodine with potassium permanganate in acetone.

The reactions in the N-formyl series above, while informative and adding to the partial structure of lycopodine known at that time, did not achieve the original objective of the oxidation of the alkaloid, that is, the direct formation of the  $\alpha$ -lactam XXVI. Concurrent with the oxidation described above we had been successful in obtaining the desired lactam.

Oxidation with potassium permanganate in acetone at room temperature gave the  $\alpha$ -lactam in 24% yield. Lycopodine was recovered to the extent of 45%, while the N-formyl keto-acid II accounted for only 5% of the total product. Other neutral products were formed in low yield. These were apparently hydroxylated lactams, showing infrared maxima at 3620, 3430, 1715 and 1615  $\text{cm}^{-1}$  (in carbon tetrachloride) but were not investigated in detail.

The lactam XXVI,  $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$ , m.p.  $163^\circ$ , exhibited maxima in the infrared at 1707 and 1630  $\text{cm}^{-1}$  (in chloroform), 1710 and 1622  $\text{cm}^{-1}$  (in carbon tetrachloride) and at 1721 and 1625  $\text{cm}^{-1}$  (nujol mull). This material was identical (m.p., m.m.p., infrared) to a sample of the  $\alpha$ -lactam kindly donated by Dr. MacLean.

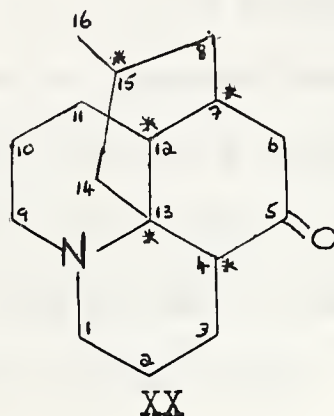
Following the proof of the constitution of lycopodine (see above) our attention turned to a study of the stereochemistry of the alkaloid, and the dehydrogenation of the lactam was not





attempted. This lactam did, however, prove useful for other purposes as will be shown later.

## II. THE STEREOCHEMISTRY OF LYCOPODINE XX.



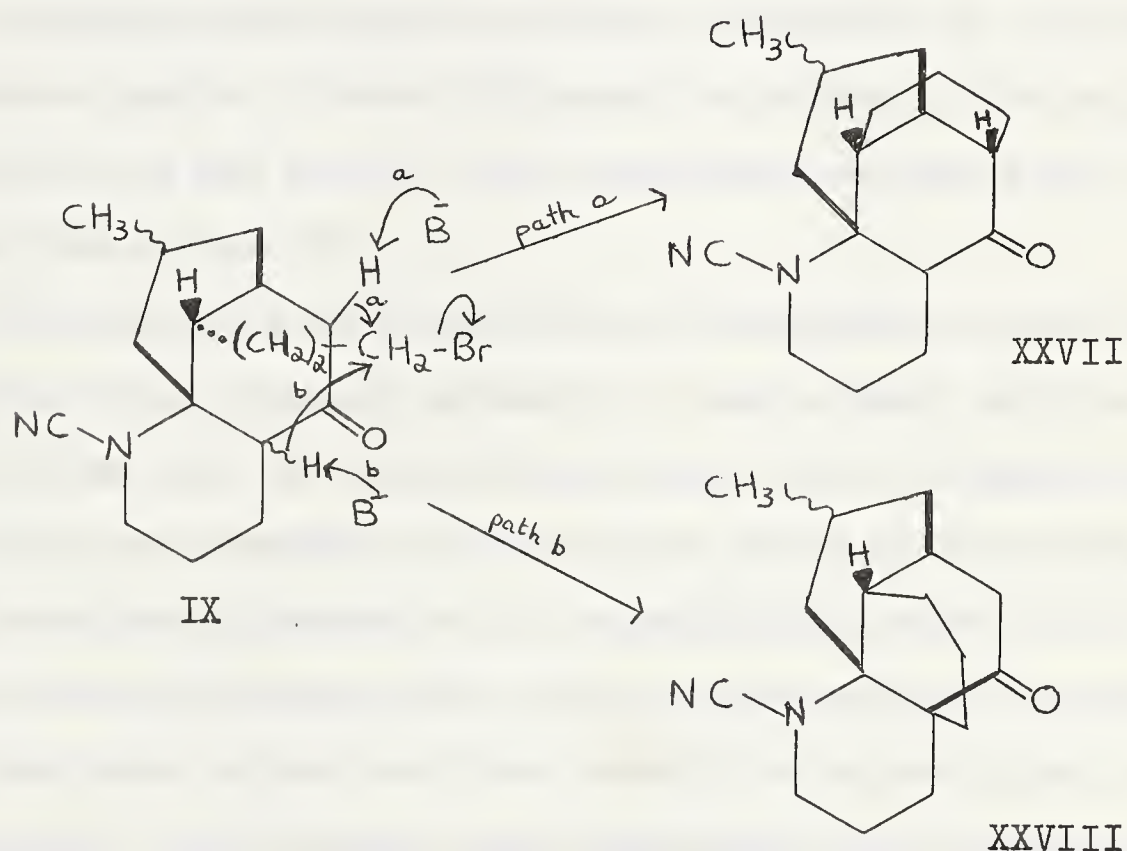
The lycopodine molecule contains five asymmetric carbon atoms (starred in figure XX) and, since the C-7 to C-13 bridge<sup>①</sup> must necessarily be cis fused, there are sixteen possible stereoisomeric forms of constitution XX.

The cis relationship between the hydrogen atom at C-12 and the C-7 to C-13 bridge could be assigned on the basis of the behaviour of  $\alpha$ -cyanobromolycopodine IX with base (40). When  $\alpha$ -cyanobromolycopodine was treated with base it lost the elements of hydrogen bromide and furnished a saturated ketone  $C_{17}H_{24}ON_2$ . This ketone which absorbed in the infrared at  $1700\text{ cm}^{-1}$  did not react with benzaldehyde, although  $\alpha$ -cyanolycopodine readily yields a benzylidene derivative (see above). On hydrolysis it gave a secondary amine which, after methylation to the tertiary amine, would not react with phenyl lithium. The carbonyl group is therefore more hindered than that in lycopodine which is attacked

.....  
<sup>①</sup> The numbering system used (see structure XX) is that suggested by K. Wiesner (73).



by phenyl lithium (40). Finally, the compound could be reduced with sodium borohydride to an alcohol which regenerated the ketone on oxidation. The loss of hydrogen bromide above without the formation of an olefinic linkage indicates that a new ring has been formed in the reaction. If the 3-bromopropyl group at C-12 is located trans to the C-7, C-13 bridge this result is easily rationalized in terms of an intramolecular C-alkylation of the ketone. The two possible modes of attack would lead to cyclic compounds XXVII and XXVIII as illustrated in the following structures. The heavy and dotted lines are used only to denote relative configurations at this point.



Later work by MacLean (44) showed that structure XXVIII represents the "cycloketone". He showed that the molecule readily incorporates two atoms of deuterium on deuterium exchange which would be expected for structure XXVIII but not for XXVII.

The cyclization, as stated already, proves that the hydrogen





atom at C-12 is cis to the C-7 to C-13 bridge.

Our attention now turned to the stereochemistry at C-4 and at C-15.

The configuration of the hydrogen atom at C-4 was determined by a study of the reduction products from lycopodine. Three reduction products have been made, each in high yield.

Lycopodine, on reduction with lithium aluminum hydride in ether or sodium borohydride in methanol, gave the alcohol dihydrolycopodine XXIX in 98 and 77% yields respectively. The free base, as reported earlier (15), melted at 167-168°, and the perchlorate at 226°.

Lithium-liquid ammonia-methanol reduction of lycopodine furnished another alcohol XXX which we called  $\alpha$ -dihydrolycopodine, m.p. 133°, in 91% yield. The perchlorate melted at 246° and the methiodide at 261-263°.

Both alcohols XXIX and XXX gave lycopodine in good yield on oxidation with chromium trioxide in acetic acid, proving that they differ only in the configuration of the hydroxyl groups.

Complete removal of the carbonyl group of lycopodine, using the Barton modification of the Huang-Minlon reduction (55), gave dihydrodeoxylycopodine XXXI which we have called "lycopodane". The free base, which could not readily be crystallized, slowly decomposed. Purification was accomplished by conversion to the perchlorate, m.p. 225°, or to the methiodide, m.p. 288°. The infrared spectrum of the perchlorate of "lycopodane" (nujol mull) was almost identical to that of the perchlorate of Alkaloid L-4, kindly donated by Dr. Marion. The melting point on admixture of the two samples showed no depression. The only difference in





the infrared spectra was the presence of a band at  $3500\text{ cm}^{-1}$  in the L.4 spectrum which was absent in lycopodane perchlorate. This could be due to water of crystallization, however, the perchlorate of XXX crystallizes even from water without water of crystallization. Thus it was not definitely proven that the two samples were identical. Lack of sufficient alkaloid L.4 prevented comparison of solvent spectra or comparison of the free bases.

Returning now to the two epimeric alcohols XXIX and XXX, infrared spectra suggested that XXIX is the equatorial epimer since XXIX exhibits relatively strong maxima at  $985\text{ cm}^{-1}$  (in carbon tetrachloride) and at  $993\text{ cm}^{-1}$  (nujol mull) while XXX has corresponding peaks at  $1030\text{ cm}^{-1}$  and  $1040\text{ cm}^{-1}$  in carbon tetrachloride and nujol respectively (56). Dissolving metal reduction would be expected to give the equatorial (i.e. most stable) isomer (57) while lithium aluminum hydride would involve attack of the reducing species from the least hindered side (58). It is of interest to note that both the dissolving metal and hydride reductions appear to be highly stereospecific in these cases. Infrared spectra of the mother liquors from the crystallization of either alcohol revealed no trace of the epimer.

Definitive proof of the configuration of the hydroxyl groups in dihydrolycopodine XXIX and  $\alpha$ -dihydrolycopodine XXX was required since the proof of the stereochemistry at the adjacent carbon C-4 depends, as shown below, on this knowledge.

Acetylation of XXIX and XXX under identical conditions indicated that XXX forms the ester more rapidly than XXIX. In fact, the acetate XXXII of  $\alpha$ -dihydrolycopodine XXX was prepared in good





yield in acetic anhydride-pyridine at room temperature for 23 hours. Under the same conditions the epimeric acetate XXXIII was formed from dihydrolycopodine XXIX only to a small extent and was best prepared by heating XXIX at  $100^{\circ}$  in acetic anhydride-pyridine.

Both acetates XXXII and XXXIII showed maxima in the infrared at  $1740\text{ cm}^{-1}$  (in carbon tetrachloride) and at  $1726$  and  $1738\text{ cm}^{-1}$  respectively (nujol mull). The perchlorate of XXXII, which showed a maximum at  $1732\text{ cm}^{-1}$  in the infrared (nujol mull), melted at  $276-278^{\circ}$  while the free base melted at  $74-76^{\circ}$ , although the latter could not readily be crystallized. The epimeric acetate XXXIII melted at  $97-98^{\circ}$ , as reported earlier (15). The hydrobromide, which showed a maximum in the infrared at  $1732\text{ cm}^{-1}$  (nujol mull), melted at  $259-262^{\circ}$  and the perchlorate melted at  $230^{\circ}$ . This perchlorate showed the ester carbonyl stretching vibration at  $1685\text{ cm}^{-1}$  (nujol) in the infrared. No explanation is offered for this unusually low ester absorption other than the suggestion that this is some function of crystal structure in the salt. The free base XXXIII was regenerated from this perchlorate on basification and chloroform extraction, proving that no unexpected rearrangement had occurred on perchlorate formation.

The relative rates of acetylation of XXIX and XXX suggest (59) that XXIX is the axial alcohol. The NMR spectra of the acetates XXXII and XXXIII were in agreement with the assignments. The acetate XXXIII of dihydrolycopodine XXIX showed peaks at  $9.08\tau$  (doublet,  $J = 6.0$  c.p.s., attributed to  $\text{CHCH}_3$ ),  $7.96\tau$  (singlet,  $\text{OCOCH}_3$ ) and a triplet centered at  $4.90\tau$  (1H, attributed to C-5 hydrogen). The epimeric acetate XXXII showed corresponding peaks at  $9.09\tau$  (doublet,  $J = 5.7$  c.p.s.),  $7.95\tau$  (3H singlet) and a one-





proton multiplet centered at 4.98 $\tau$ . Thus in the equatorial acetate the axial proton does absorb at higher field than the equatorial proton in the epimers, in agreement with the findings of Lemieux, Kullnig, Bernstein and Schneider (94), and Shoolery and Rogers (95), which show that in six-membered ring systems the axial proton in an epimeric pair is usually at higher field than the equatorial.

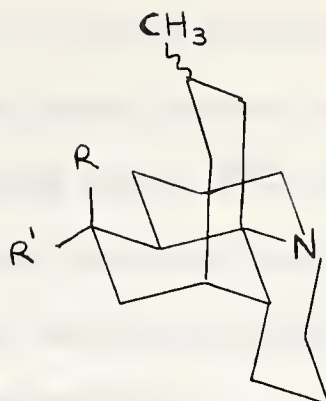
The configurations of the hydroxyl groups in the epimeric acetates XXIX and XXX were established with certainty when attempts were made to convert each alcohol to the corresponding cathylate.

The alcohol XXX,  $\alpha$ -dihydrolycopodine, readily formed the cathylate XXXIV,  $C_{19}H_{31}O_3N$ , on treatment with ethyl chloroformate in pyridine at room temperature. The oily base was purified as the methiodide, m.p. 233 $^{\circ}$ , which showed a maximum in the infrared at 1732  $cm^{-1}$  (nujol mull). Treatment of XXXIV with perchloric acid in acetone led to rapid hydrolysis and the isolation of the perchlorate of the parent alcohol XXX.

The alcohol XXIX, dihydrolycopodine, was recovered unchanged after attempted cathylation under identical conditions. It is thus (60) highly probable that  $\alpha$ -dihydrolycopodine XXX, is the equatorial alcohol, while XXIX is the axial epimer.

In order to simplify the discussion the hydrogen at C-4 will now be placed trans to the C-7, C-13 bridge. That this is the correct orientation at C-4 is demonstrated below. The compounds above can now be represented by the following structures.





XXIX	R = OH ; R' = H
XXX	R = H ; R' = OH
XXXI	R = R' = H
XXXII	R = H ; R' = OAc
XXXIII	R = OAc ; R' = H
XXXIV	R = H ; R' = OCOOEt
XXXVI	R or R' = Cl

Dehydration of dihydrolycopodine XXIX using phosphorus pentachloride in refluxing xylene (15) or phosphorus oxychloride-pyridine at room temperature gave anhydrodihydrolycopodine XXXV. The phosphorus oxychloride procedure was by far the more efficient giving the olefin in 78% yield.

The olefin XXXV was a colorless labile oil which could not be crystallized and which slowly decomposed. The perchlorate melted at 235-237°, as reported earlier (15). The NMR spectrum of the perchlorate of XXXV showed a peak at 4.26 $\tau$ , enclosing an area almost exactly equal to one third of that under the peak at 9.04 $\tau$  (doublet J= 5.5 c.p.s.), attributed to  $>\text{CH}-\text{CH}_3$ . Thus the olefin anhydrodihydrolycopodine contains a tri-substituted double bond, which must be between C-4 and C-5. Since this olefin was prepared by dehydration of the axial alcohol XXIX, then the hydrogen lost from C-4 is presumably axial (57).

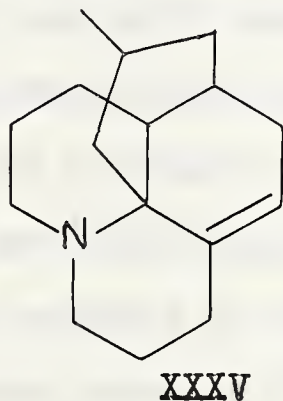
Treatment of the equatorial alcohol XXX with phosphorus oxychloride-pyridine, under conditions identical to those used for the conversion XXIX  $\longrightarrow$  XXXV above, afforded the chloro compound





XXXVI in 70% yield. The free base XXXVI melted at 92-94° after sublimation and the perchlorate at 230-231°. The fact that XXIX is readily dehydrated while XXX gives a chloro compound on treatment with phosphorus oxychloride-pyridine further substantiates our conclusion that XXIX and XXX are the axial and equatorial alcohols respectively (61).

The perchlorate of the anhydro compound XXXV could not be hydrogenated to the hydrocarbon XXXI although several attempts, using platinum, palladium and rhodium catalysts, were made. Approach of the catalyst to the double bond is highly hindered on both sides, thus preventing hydrogenation.



It was hoped that Brown hydration (62), which is known to proceed by overall cis anti-Markownikoff addition, of XXXV would give  $\alpha$ -dihydrolycopodine XXX, thus affording definitive proof of the orientation of the hydrogen atom at C-4. Treatment of anhydro-dihydrolycopodine (XXXV) with diborane, produced in situ from boron trifluoride etherate and lithium aluminum hydride, gave a compound XXXVII, m.p. 144°, in 81% yield. Analysis showed that XXXVII contained one boron atom per molecule, while infrared spectra showed maxima at 2360, 2325 and 2275  $\text{cm}^{-1}$  (nujol mull) attributed (63) to B-H stretching vibrations. It appeared, however,





that addition had not occurred across the olefinic double bond, since the infrared spectrum also showed peaks at 822 and 812  $\text{cm}^{-1}$ , indicative of a double bond. This finding was not surprising, since attack by the basic nitrogen on the acidic diborane might be expected and since the olefinic linkage is known to be severely sterically hindered (for example, anhydrodihydrolycopodine perchlorate could not be reduced catalytically (see above)). In agreement with these views treatment of the boron compound with hydrogen peroxide in ethanolic sodium hydroxide gave the anhydro compound XXXV. In some cases an oxygenated compound was also produced, usually together with XXXV.

The new oxygenated compound appeared to exist in two crystalline forms, m.p.  $61^{\circ}$  and  $107^{\circ}$ , while the perchlorate melted at  $215^{\circ}$ . The lack of hydroxyl and carbonyl absorption in the infrared, together with the presence of an olefinic double bond (infrared maximum at 812  $\text{cm}^{-1}$ ) and the molecular formula  $\text{C}_{16}\text{H}_{25}\text{ON}$ , suggested that this compound is the N-oxide XXXVIII of the olefin XXXV and that the boron atom in XXXVII is, in fact, attached directly to the nitrogen atom.

This view was substantiated by the fact that XXXV was produced on treatment of the boron-containing compound with ethanolic sodium hydroxide without hydrogen peroxide, and proved by a study of the NMR spectrum of the boron compound XXXVII. The latter showed a poorly defined doublet at 9.08 $\tau$  ( $J \approx$  approx. 2.5 c.p.s., 3H signal attributed to  $\text{CH}-\text{CH}_3$ ) and a broadened singlet (1H) at 4.39 $\tau$  attributed to the olefinic proton at C-5.

In further attempts to relate the two epimeric alcohols or their derivatives and thus confirm the stereochemistry at C-4



inferred from the dehydration experiments above, attempts were made to pyrolyze the acetates XXXII and XXXIII.

If the hydrogen at C-4 is, in fact, axial, as suggested already, then pyrolysis of the equatorial acetate XXXIII would be expected to give the anhydro compound XXXV while the axial acetate XXXII should give the disubstituted olefin XXXIX, as yet unreported. Pyrolysis of acetates is known (64,65) to give the olefin by cis elimination.

However, neither reaction was successful. At low temperatures both epimers distilled unchanged while at higher temperatures virtually complete breakdown occurred. Small quantities of starting material were detected, but no other products could be distilled from the charred residues. Temperatures ranging from 80° to 620° were used for the several attempts.

Interrelationship of the two series was finally achieved by pyrolysis of the xanthate methiodide XL of the equatorial alcohol XXX. The xanthate was prepared by refluxing the alcoholate of XXX, produced by refluxing XXX with sodium in dry ether for sixty hours, with excess carbon disulphide for twenty hours. Excess methyl iodide was added and the mixture refluxed for a further twenty-four hours. After crystallization from ethanol XL melted at 280-282° and showed maxima in the infrared at 1235, 1220 and 927 cm<sup>-1</sup>.

The xanthate methiodide slowly melted on heating at atmospheric pressure at 265°. Vacuum distillation of the residual oil gave a colorless oil which was converted to the perchlorate in acetone and crystallized from acetone-ether. This perchlorate was found to be identical in all respects ( m.p., m.m.p., infrared ) to the perchlorate of an authentic sample of anhydrodihydro-



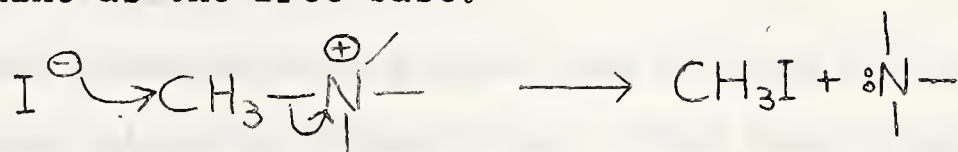




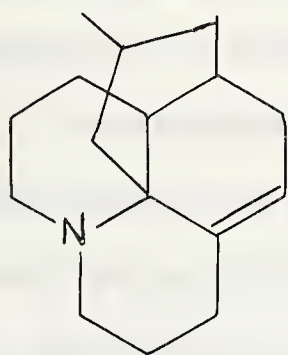
lycopodine XXXV.

Since xanthate pyrolysis is known (65) to proceed via cis-elimination, the hydrogen atom at C-4 must be cis to the C-5 xanthate group. The latter has been proved to be equatorial (see above) thus the C-4 hydrogen must be axial.

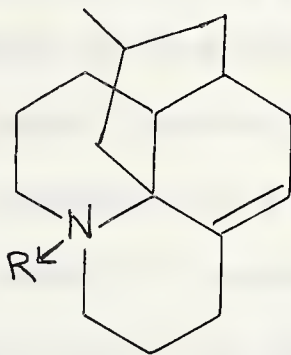
The fact that the methiodide XL yields the free base XXXV on pyrolysis is not unusual. The methiodides of lycopodine XX and of the alcohol XXX both give the parent free base on vacuum distillation at 200°. The reaction is essentially a nucleophilic attack by iodide on the methyl carbon with displacement of the tertiary amine as the free base.



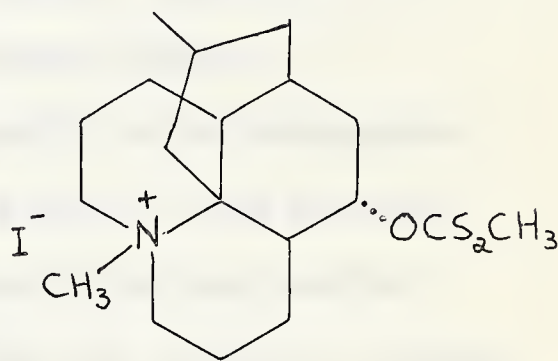
The compounds mentioned above can be represented by the following structures:



XXXV



XXXVII, R=BH<sub>3</sub>  
XXXVIII, R=O



XL

The reduction of the lactam XXVI was studied in a manner similar to that described above. The lactam gave rise to three reduction products, each in high yield under the appropriate conditions.

Reduction with lithium aluminum hydride in ether gave a mixture of starting material and a hydroxy lactam XLI. With excess



hydride a mixture of XLI and dihydrolycopodine XXIX was obtained. Reduction of the lactam with lithium aluminum hydride in refluxing tetrahydrofuran gave dihydrolycopodine in high yield. Finally, reduction with sodium borohydride in methanolic sodium hydroxide gave the hydroxy lactam XLI in high yield. The reduction product XLI, m.p. 189-190°, showed maxima in the infrared at 3500, 3400 and 1610  $\text{cm}^{-1}$ .

Lithium-ammonia-methanol reduction of the keto-lactam XXVI gave a different hydroxy lactam XLII, m.p. 253-254°, exhibiting infrared maxima at 3350 and 1612  $\text{cm}^{-1}$  (nujol) and at 3625, 3400 and 1613  $\text{cm}^{-1}$  (chloroform).

It seems reasonable to assume that XLI and XLII are the axial and equatorial alcohols respectively, since under similar reducing conditions lycopodine yielded the axial and equatorial alcohols XXIX and XXX respectively. This conclusion is supported by the observation in the reduction results above that the hydroxy lactam XLI is the precursor of the axial alcohol XXIX.

Dehydration of the axial hydroxy lactam XLI with phosphorus oxychloride in pyridine resulted in a good yield of the dihydrodeoxylactam XLIII, m.p. 116-117°, which showed infrared maxima at 1640 and 818  $\text{cm}^{-1}$ , attributed to the amide and olefinic linkage respectively.

The equatorial alcohol was converted to the corresponding xanthate XLIV in a manner similar to that described above for the preparation of the xanthate methiodide XL. The xanthate XLIV, m.p. 154-155°, showed maximal absorption in the infrared at 1642  $\text{cm}^{-1}$  (attributed to the amide group) and at 1235, 1218 and 1048  $\text{cm}^{-1}$  (xanthate group).

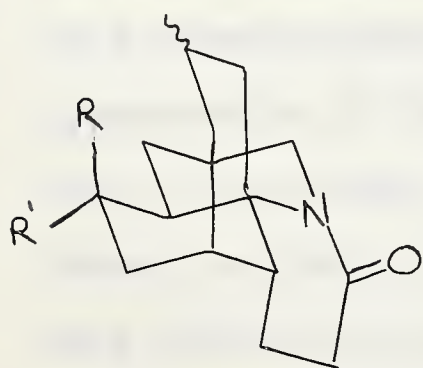




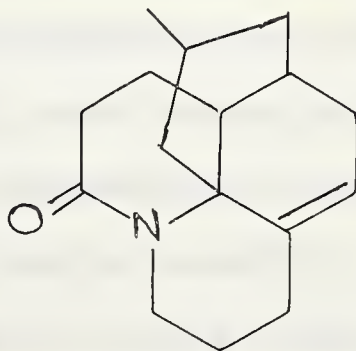
Pyrolysis of the xanthate XLIV at 200° for two minutes at atmospheric pressure gave a colorless oil which yielded a colorless solid after vacuum distillation. The product melted at 117-118° and showed no melting point depression after admixture with the anhydrolactam XLIII. Infrared spectra, however, although almost identical, suggested that the disubstituted olefin XLV may also have been formed during the pyrolysis of the xanthate XLIV, since the pyrolysis product showed absorption at 752 cm<sup>-1</sup> not present in XLIII. Nuclear Magnetic Resonance spectra of the two materials showed peaks at 9.09 $\tau$  (doublet, J = 5.5 c.p.s.), attributed to  $\text{>CH-CH}_3$ , together with a one proton signal at 4.60 $\tau$  (side band at 4.47 $\tau$ ) attributed to the olefinic proton. The intensity of the peak at 4.47 $\tau$  was, however, greater in the dehydration product perhaps due to the disubstituted olefin XLV.

The sequence of reactions above again indicated that the hydrogen atom at C-4 is axial, although, largely because of the difficulties experienced in the purification of the several neutral compounds, the proof is not as rigorous as that described earlier for the basic series.

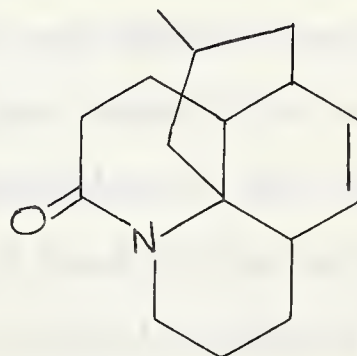
The compounds in the lactam series can now be represented by the following structures:



XLI, R = OH : R' = H  
 XLII, R = H : R' = OH  
 XLIV, R = H : R' = OCS<sub>2</sub>CH<sub>3</sub>



XLIII

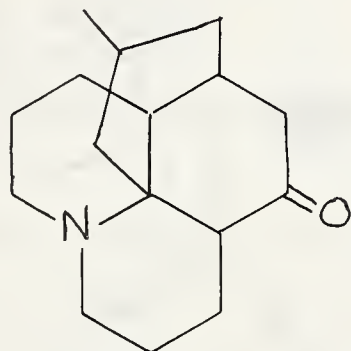


XLV

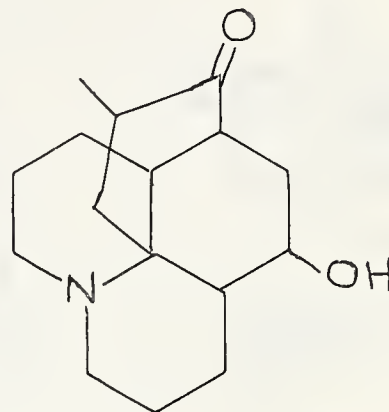




With the configuration at C-4 established the only remaining points are the stereochemistry at C-15, the carbon bearing the methyl group and the absolute configuration. This problem has been discussed by Anet (66) who studied the relationship between lycopodine XX and annofoline XLVI (33).



XX



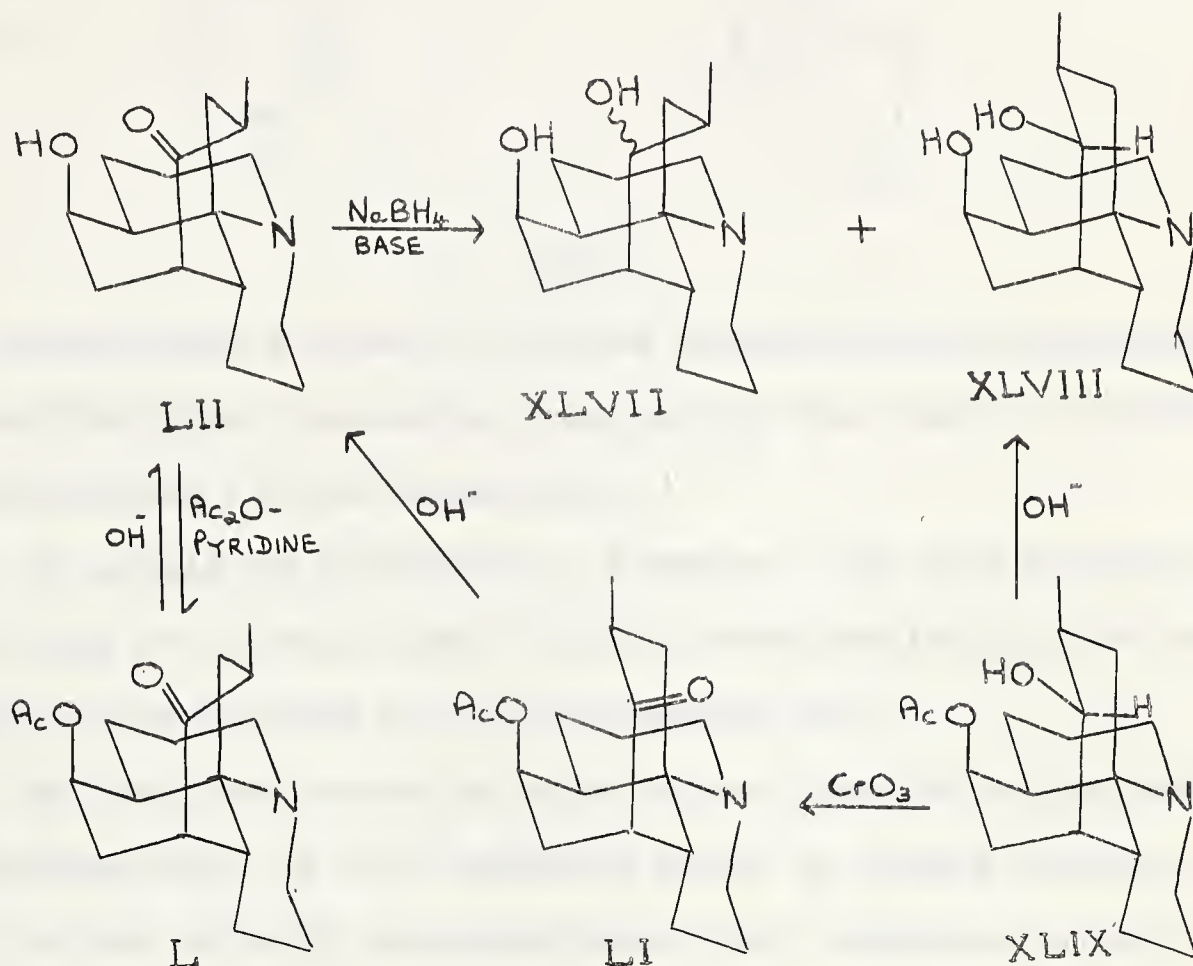
XLVI

Anet found that reduction of annofoline with sodium borohydride in neutral media or with lithium aluminum hydride in ether yielded a diol XLVII which he called  $\alpha$ -dihydroannofoline. Reduction of annofoline with sodium borohydride in basic solution gave a mixture of XLVII and another diol,  $\beta$ -dihydroannofoline XLVIII, the latter identical to the deacetyl derivative of fawcettine XLIX (30).

The  $\beta$ -isomer is not a reduction product of annofoline, but of a ketone having the methyl group in the opposite configuration to that of annofoline. This was confirmed by the non-identity of O-acetylannofoline hydrobromide L.HBr and dehydrofawcettine hydrobromide LI.HBr, even though both gave annofoline on hydrolysis (46). This means, presumably, that annofoline is the stable isomer, but under alkaline conditions it must be isomerized to some extent to the less stable isomer, which is reduced faster than annofoline. Annofoline exists as a mixture of the hemiketal and the internally hydrogen bonded hydroxy ketone forms. The



bridge ring must therefore be in the boat conformation, with the methyl group presumably equatorial, as illustrated in structure LII. The reactions described above are illustrated by the following structures.

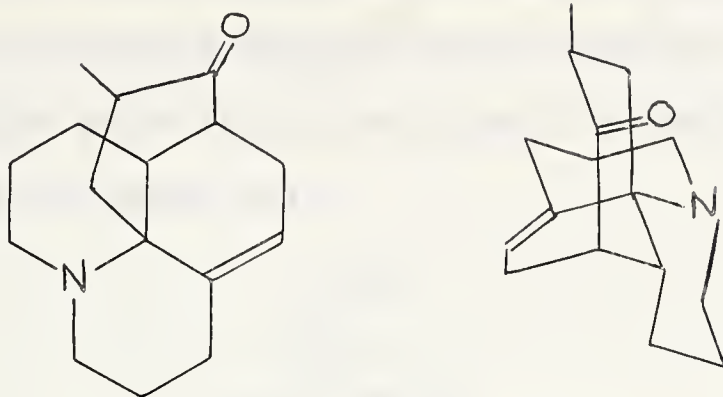


Anet points out (66) that if the hydroxyl were not present at C-5, or even more if a double bond was present between C-5 and either C-4 or C-6, then the chair form of the bridge ring D would be preferred, since there would then be no steric repulsion between C-15 and the C-5 axial substituent. In this conformation which is, presumably, that found in the epimeric ketone mentioned above the most stable conformation has the methyl group equatorial to the chair form of the D-ring. By a similar argument therefore, Anet states that compound LIII, prepared earlier from fawcettiine by Burnell (30), must also have the ring D in the chair conformation





with the methyl group equatorial.



LIII

The unsaturated ketone LIII gives anhydrodihydrolycopodine XXXV on Wolff-Kishner reduction, suggesting that the C-15 methyl group in lycopodine is also equatorial.

It should be pointed out, however, that Wolff-Kishner reduction does not always lead to the thermodynamically most stable epimer at the carbon  $\alpha$  to the carbonyl (67).

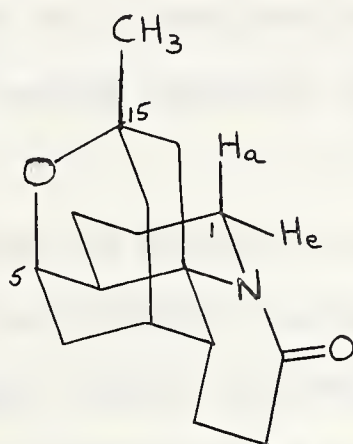
We have now proved by more direct chemical means that the stereochemistry at C-15 inferred above is indeed correct.

It has already been mentioned that reduction of the lactam XXVI with sodium borohydride gives the axial hydroxy lactam XLI in good yield. The hydroxy compound shows a peak in the NMR at 9.12 $\tau$  (3H doublet,  $J = 6.5$  c.p.s.) attributed to  $\text{CHCH}_3$ .

Oxidation of XLI with lead tetraacetate in refluxing benzene gave a compound, m.p. 178-180°, which analyzed for  $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$ , indicating the loss of two hydrogens from the starting material. The molecular weight of 261 was confirmed by mass spectrum. The oxidation product showed strong absorption in the infrared at 1630  $\text{cm}^{-1}$  (in carbon tetrachloride) and at 1620  $\text{cm}^{-1}$  (nujol), but no other carbonyl absorption and no hydroxyl absorption. The second oxygen atom is therefore present as part of an ether

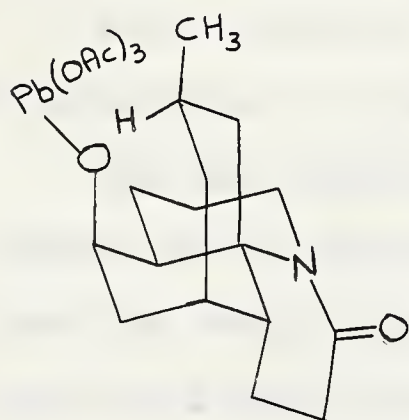


linkage. The NMR spectrum of this ether showed a three proton signal at  $\delta$  8.78 $\tau$ , attributed to the methyl group. The fact that this signal is a sharp singlet means that the carbon carrying the methyl is fully substituted and thus the oxidation product must be the C-5, C-15 ether LIV.

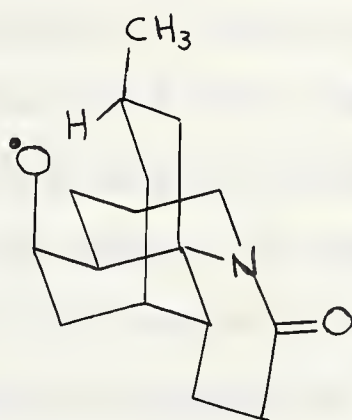


LIV

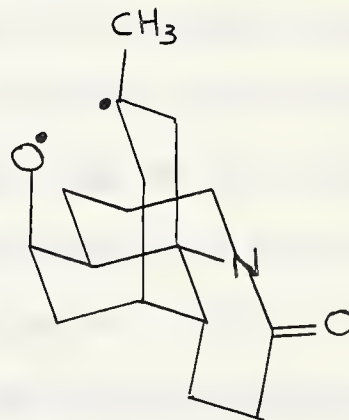
Several examples of cyclic ether formation by this method have been reported (68). In our case the ether LIV is formed in better than 90% yield. The reaction presumably proceeds via the intermediate LV which could then cleave by two conceivable mechanisms:



LV



LVI



LVII

(a). Homolytic cleavage to give LVI, together with lead diacetate and an acetoxy radical. Abstraction, by this acetoxy radical or by a methyl radical formed by loss of carbon dioxide





from the acetoxy radical, of the hydrogen atom from C-15 leads to the di-radical LVII, which could close to the ether LIV.

(b). Heterolytic cleavage of the oxygen-lead bond in LV to give an oxonium ion (LVI,  $-O^{\bullet}$  replaced by  $-O^+$ ). The latter could abstract a hydride ion from C-15, giving a hydroxy carbonium ion (LVII,  $-O^{\bullet}$  replaced by  $-OH$ ; tertiary radical replaced by tertiary carbonium ion), which would close to give the protonated form of the ether LIV.

Two conclusions can be drawn from this reaction. Firstly, in the lactam series the bridge ring must be present at least to some extent in the chair form, otherwise the C-15 hydrogen would be too far from the C-5 oxygen atom for the cyclization to occur. Secondly, the C-15 hydrogen must be axial. Although the exact mechanism of the reaction is not known it seems highly unlikely that hydrogen removal from C-15 would occur so smoothly unless the bridge ring approximated the chair form and unless the C-15 hydrogen were axial.

The oxidation, therefore, shows that the C-15 methyl group in lycopodine is equatorial to a ring approximating the chair form.

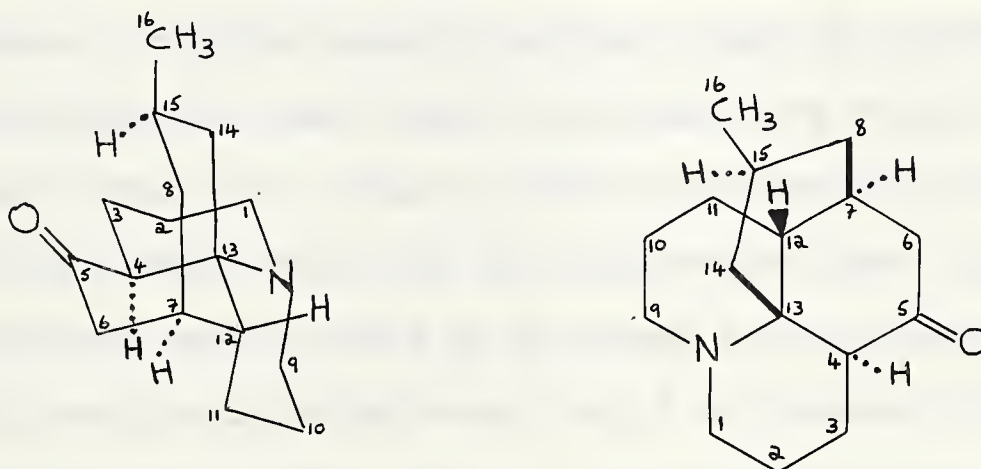
The NMR spectra of the dihydrolactam XLI and of the ether LIV showed several interesting peaks. It has already been mentioned that the methyl signal in LIV was sharp singlet at  $8.78\tau$ . The shift to lower field from the doublet at  $9.12\tau$  (splitting 6.5 c.p.s.) in XLI is expected on ether formation (69). The hydroxy lactam XLI and the 5-15 ether LIV also showed doublets at  $5.54\tau$  ( $J = 12$  c.p.s.) and  $5.42\tau$  ( $J = 14$  c.p.s.) respectively. These one-proton signals are attributed to hydrogen on C-1 (see structure LIV above). The proton designated  $H_e$  is in the shielding region of the amide





system, strongly coupled to the axial proton  $H_a$ . The equatorial proton  $H_e$ , which is responsible for the low field absorption, is eclipsed by the carbonyl group of the amide with a separation of  $2.4 \text{ \AA}$  (from Dreiding models). The axial proton  $H_a$  gives a signal at  $7.18\tau$ . This was shown by spin decoupling experiments. Irradiation at this frequency caused the doublet at  $5.42\tau$  to collapse to a broadened singlet. The singlet at this point is not sharp because  $H_e$  is also coupled to the protons on C-2.

On the basis of the results outlined above the complete relative stereochemistry of lycopodine can be illustrated with structure LVIII.



LVIII

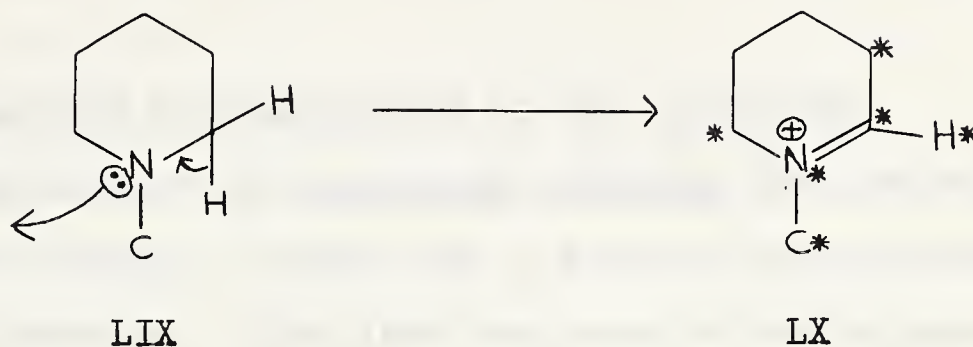
The absolute stereochemistry has been determined by application (74) of the octant rule to lycopodine. This will be discussed in some detail later (see page 50).

Consideration of the structure LVIII readily explains the observations that oxidation to the N-formyl acid II and to the lactam XXVI occurs in the so-called  $\alpha$ -ring, that is, by cleavage of the 9,10 bond to give II and by introduction of oxygen at C-9 to give XXVI.

The initial step in the oxidation of lycopodine is presumably

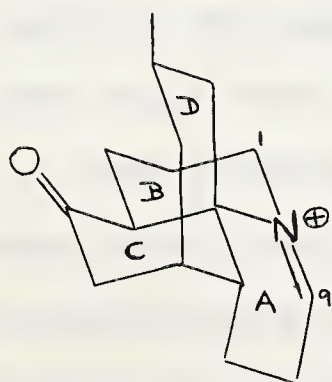


oxidative attack at the nitrogen, with proton loss from an adjacent carbon, as indicated in LIX  $\longrightarrow$  LX.

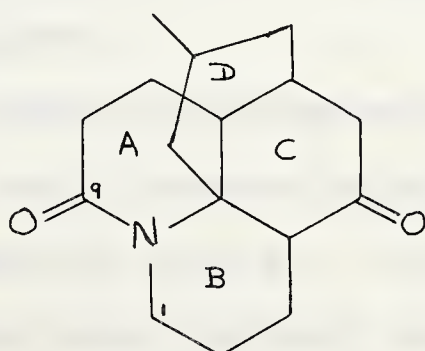


An intermediate of type LX could then lead to either the N-formyl acid II or to the lactam XXVI.

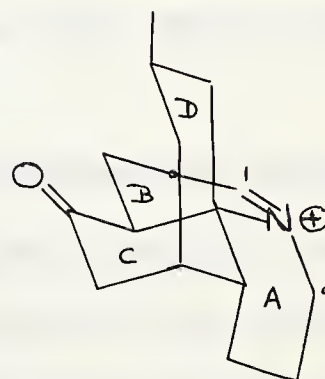
The atoms indicated by the asterisks in LX must lie in the same plane. Dreiding models indicate that the intermediate LXI, produced by proton loss from C-9, would have rings B, C and D in the chair form, while ring A, which includes the nitrogen-carbon double bond, would exist in the half-chair form. The intermediate LXII, however, which would be produced if the proton were lost from C-1 could only exist with ring A in the boat form and ring B in the half-chair form, because of the requirement that the six starred atoms in LX be co-planar.



LXI



XXVI



LXII





Since the intermediate LXI is thus presumably of lower energy than LXII, oxidation will occur toward C-9, explaining the observed  $\alpha$ -lactam formation and agreeing with our earlier conclusion that the N-formyl acid is formed by cleavage of the  $\alpha$ -ring.

### III. EXTRACTION AND SEPARATION OF THE ALKALOIDS.

The alkaloids of Lycopodium clavatum Linn. have been studied by several workers (2,7,32) and a total of ten alkaloids reported in the literature. The plant has been re-investigated in these laboratories, but only three (lycopodine, flabelliformine, and clavolonine) of the previously reported bases were isolated. However, seven other alkaloids were isolated. Of these, four (lycodoline, lycodine,  $\alpha$ -obscurine and de-N-methyl- $\alpha$ -obscurine) have been described in another report (26). The other alkaloids were shown to be dihydrolycopodine, a 1:1 molecular complex of dihydrolycopodine and flabelliformine, and a hydroxy acetate,  $C_{18}H_{29}O_3N$ , which we named lycoclavine. The structure and stereochemistry of lycoclavine are reported below.

We have also isolated the above mentioned molecular complex from Lycopodium flabelliformine.

We have also investigated the alkaloidal content of Lycopodium clavatum var megastachyon Fern. and Bissel (43), which had not previously been studied.

Two closely related alkaloids were isolated and their structures established. One of these alkaloids was found to be identical to lycoclavine, mentioned earlier. In addition five other alkaloids of known constitution were isolated, along with a small amount of a base of undetermined structure.



The total crude alkaloid of Lycopodium clavatum var megastachyon, obtained by methanol extraction of the finely ground plant, amounted to approximately 0.12% of the dry weight of the plant. Separation of the alkaloids, achieved mainly by chromatographic techniques, (see Experimental), yielded the following compounds:

- (i) Lycopodine -- 30% of the total basic material
- (ii) Clavolonine -- 11%
- (iii) Lycoclavine, m.p. 212-213° -- 7.5%
- (iv) A compound,  $C_{20}H_{31}O_4N$ , m.p. 144-145° -- 11%, which proved to be the O-acetyl derivative of lycoclavine.
- (v) A substance,  $C_{32}H_{52}O_3N_2$ , m.p. 213-214° -- 1.5%, which was shown to be a 1:1 complex of dihydrolycopodine ( $C_{16}H_{27}ON$ ) and flabelliformine ( $C_{16}H_{25}O_2N$ ).
- (vi) O-Acetyl dihydrolycopodine -- 1%
- (vii) In addition to the above mentioned alkaloids a small amount of an apparently new alkaloid, m.p. 261-263°, analyzing best for  $C_{16}H_{25-27}O_2N$ , was also isolated. The Mass Spectrum of this alkaloid (which will be discussed in more detail later) showed that the molecular weight was 263, proving that the molecular formula is, in fact,  $C_{16}H_{25}O_2N$ .

The structures of lycopodine (44), flabelliformine (45), and clavolonine (46) are now known. Furthermore, a comparison of the infrared spectra of clavolonine and of alkaloid L.34, first reported by Manske in 1953 as an alkaloid of Lycopodium densum Labill (11), revealed their identity.

The composition of the molecular complex in (v) above was established in the following manner. Attempts to separate the





complex by fractional crystallization and by chromatography were unsuccessful. However, treatment of the complex with chromium trioxide in pyridine oxidized the dihydrolycopodine to lycopodine and left the flabelliformine unchanged (26). The two components were then easily separable by chromatography. Finally, combination of equimolar quantities of dihydrolycopodine and flabelliformine gave a high yield of the C-32 complex, identical (m.p., m.m.p., infrared) with that obtained from the plant. It is interesting to note that flabelliformine also forms stable 1:1 complexes with lycopodine and lycodoline, although these are readily separable by chromatography (26).

#### IV. THE CONSTITUTION AND STEREOCHEMISTRY OF LYCOCLAVINE.

Following the elucidation of the stereochemistry of lycopodine, our attention turned to the minor alkaloids of Lycopodium clavatum var. megastachyon. One of these, which we named lycoclavine, had apparently not been previously reported, although we had also isolated it from Lycopodium clavatum Linn. (see above).

Lycoclavine was isolated from the plant to an extent of about 0.01% w/w of the dried plant material. The purification of the alkaloid is complicated somewhat by the fact that lycoclavine and clavolonine tend to be eluted together on chromatography over alumina. Careful chromatography, however, gives pure lycoclavine, which crystallizes as long colorless needles, m.p. 212-213°, from acetone.

Another less polar alkaloid, isolated from the plant in approximately 0.014% overall was shown (see below) to be the O-acetate of lycoclavine.





(a) The relationship between lycoclavine and acetyllycoclavine.

Lycoclavine was found to have the molecular formula  $C_{18}H_{29}O_3N$ . The presence of a hydroxyl and an acetoxyl group was established by the following observations. The infrared spectrum of the alkaloid (in dilute carbon tetrachloride) showed a concentration independent peak at  $3600\text{ cm}^{-1}$ , indicative (70) of an intramolecularly hydrogen bonded hydroxyl group. Maxima at  $1736$  and  $1240\text{ cm}^{-1}$  in the infrared and at  $7.93\tau$  (three proton signal) in the NMR suggested the presence of an O-acetyl group and this was confirmed by hydrolysis to acetic acid and diol  $C_{16}H_{27}O_2N$ , henceforth called desacetyllycoclavine.

The secondary nature of these functional groups was indicated by the NMR spectrum of lycoclavine, which showed one-proton peaks at  $5.11\tau$  (doublet, splitting  $6.9\text{ c.p.s.}$ ) attributed to  $>\underline{C}HOAc$ , and at  $6.40\tau$  (singlet) attributed to  $>\underline{C}HOH$ .

Acetylation of lycoclavine or desacetyllycoclavine with acetic anhydride-pyridine yielded acetyllycoclavine,  $C_{20}H_{31}O_4N$ , m.p.  $144^\circ$ , which was also obtained directly from the plant (see above).

Both lycoclavine and acetyllycoclavine gave the diol desacetyllycoclavine on basic hydrolysis, vigorous acid hydrolysis or, better, on reduction with lithium aluminum hydride. Relatively mild hydrolysis of the diacetate with aqueous hydrochloric acid gave a better than 90% yield of lycoclavine.

The diacetate showed peaks in the NMR at  $4.92\tau$  (doublet, splitting  $6.9\text{ c.p.s.}$ ) and  $5.32\tau$  (singlet), the latter being attributed to the proton on the carbon bearing the hydroxyl group in lycoclavine.

The NMR also revealed the presence of a secondary C-methyl

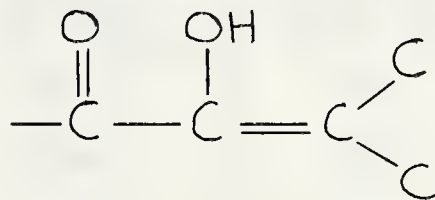




group, with doublets at 9.09 and 9.087 (splitting  $\overline{\text{ca}}$  6 c.p.s.) in lycoclavine and acetyllycoclavine respectively. Lack of NH absorption in the infrared spectra of lycoclavine and its acetyl derivative indicated the tertiary nature of the amino nitrogen. Since lycoclavine could not be reduced catalytically and showed no olefinic protons in the NMR it appeared to be tetracyclic.

(b) The carbon skeleton of lycoclavine.

Oxidation of lycoclavine with chromic acid in acetic acid, followed by chromatography over alumina, yielded a basic compound  $\text{C}_{16}\text{H}_{27}\text{O}_3\text{N}$ , m.p. 174-175°, which showed peaks in the infrared at  $1751\text{ cm}^{-1}$  (O-acetyl) and  $1724\text{ cm}^{-1}$  (cyclohexanone) and in the ultraviolet at  $282\text{ m}\mu$  ( $\log\epsilon=2.56$ ). Hydrolysis of this ketone, which we shall refer to as "lycoclavinone", with dilute sodium hydroxide, yielded an amphoteric compound,  $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$ , which had the properties of a diosphenol. In particular, the ultraviolet spectrum showed a maximum at  $282\text{ m}\mu$  ( $\log\epsilon = 3.99$ ) in neutral solution, which shifted to  $327\text{ m}\mu$  in dilute base and to  $248\text{ m}\mu$  on acetylation. These values are indicative (71) of the grouping



The formation of the enolic  $\alpha$ -diketone indicated that lycoclavinone was an  $\alpha$ -acetoxy ketone, the  $\alpha$ -diketone arising from aerial oxidation of the initially formed  $\alpha$ -ketol.

The susceptibility of  $\alpha$ -ketols to aerial oxidation in alkaline solution is well authenticated (72) and it was found that the rate of formation of the diketone (as determined by the rate of increase of the  $\epsilon$  value at  $327\text{ m}\mu$ ) was substantially reduced when the reaction





was carried out in a nitrogen atmosphere and accelerated when oxygen was bubbled through the hydrolysis solution. (See Table II). Hydrolysis of lycoclavinone with aqueous acid yielded the  $\alpha$ -ketol  $C_{16}H_{25}O_2N$ , in high yield. The ketol exists in two crystalline forms, m.p. 122-123° and m.p. 135-136°, with different nujol spectra but identical solution spectra. The  $\alpha$ -ketol underwent aerial oxidation to the diosphenol in alkaline solution. (See Table II).

These results demonstrate the presence of the grouping



flanked on at least one side by a methine group, in lycoclavine.

TABLE II

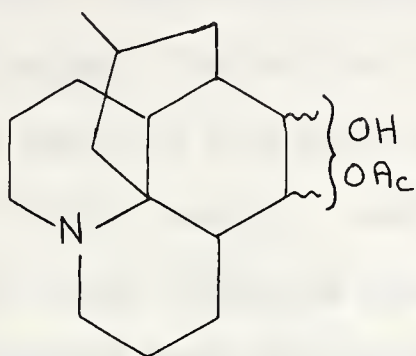
To illustrate the relative rates of formation of the diosphenol in 2% aqueous sodium hydroxide at room temperature. The values quoted are the  $\epsilon$  values at 327  $m\mu$  (pH = 14).

TIME IN MINUTES	REACTION CONDITIONS			
	Lycoclavinone			$\alpha$ -ketol
	in air	under $N_2$	under $O_2$	in air
60	2700	100	2300	3200
120	3700	700	4550	
240	4600	1350	6990	6050

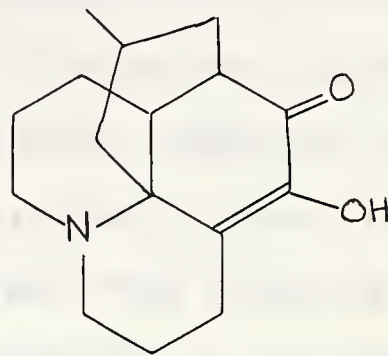
The presence of the grouping  $-CHOH-CHOAc-$ , a  $-CHCH_3$  and a tertiary nitrogen, together with the fact that lycoclavine occurs along with lycopodine (LVIII) and several other alkaloids having the lycopodine skeleton and that all Lycopodium alkaloids of known constitution bear an oxygen or its biogenetic equivalent (i.e. unsaturation or nitrogen) at C-5, suggested structure LXIII



(without stereochemical implications) as a possibility for lycoclavine and hence LXIV for the enolic  $\alpha$ -diketone.



LXIII



LXIV

In order to test this hypothesis we set out to prepare the enolic  $\alpha$ -diketone (LXIV) directly from lycopodine.

(c) Preparation of the diosphenol LXIV from lycopodine.

The initial route chosen for the conversion of lycopodine to the 5,6 diketone was via the 6-bromo ketone.

In 1956 Barclay and MacLean reported (42) that the bromination of lycopodine in carbon tetrachloride yielded a monobrominated product, isolated as the hydrobromide m.p. 290-295°(dec). Attempts to isolate the free base were unsuccessful.

In our hands treatment of lycopodine with an equimolar amount of bromine in either carbon tetrachloride or chloroform without added hydrogen bromide led to the isolation of a crystalline product, which proved to be a mixture of lycopodine hydrobromide and monobromolycopodine hydrobromide. The melting point of this mixture (285-295°, dec), corresponds to that reported by the earlier workers (42) but differs considerably from that of the pure bromolycopodine hydrobromide (see below). The composition of the crystalline product was determined in the following manner. The analytical results obtained on a recrystallized sample fitted





best for an approximately 1:1 mixture of lycopodine hydrobromide and monobromolycopodine hydrobromide. Treatment of the mixture with aqueous sodium hydroxide at room temperature, followed by chromatography, led to the isolation of lycopodine, in about 50% yield, as well as the enolic  $\alpha$ -diketone LXIV, identical in all respects (m.p., m.m.p., infrared, ultraviolet, optical rotation at 589 m $\mu$ ) to that obtained from lycoclavine. The diketone LXIV was later prepared from the pure 6 $\alpha$ -bromolycopodine, whose preparation and properties will be discussed later.

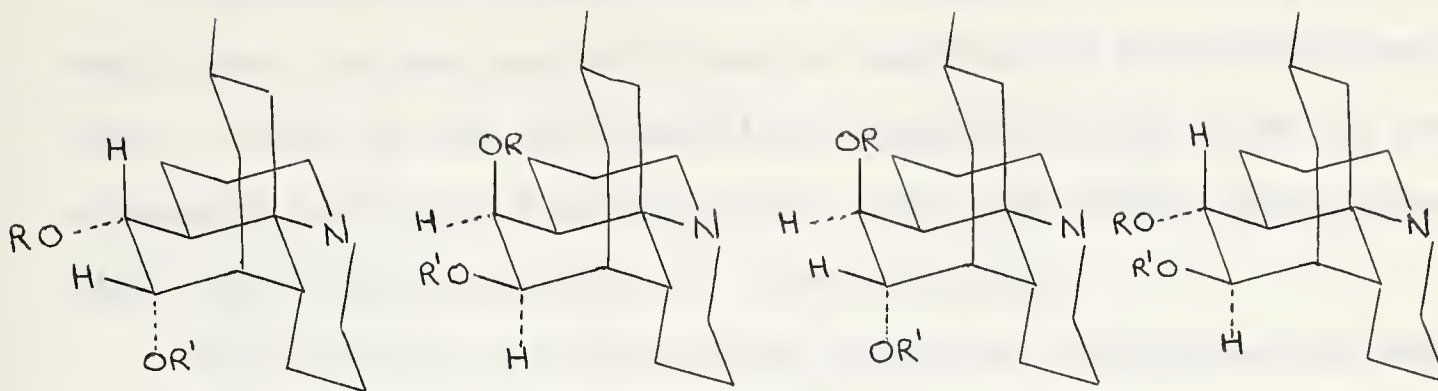
The diketone LXIV was best prepared, however, by direct oxidation of lycopodine with one mole of selenium dioxide in refluxing dioxane, which gave, in addition to unchanged lycopodine, the diketone LXIV in 25% yield. Use of excess selenium dioxide in either refluxing dioxane or 90% acetic acid led to the formation of compound(s) absorbing at 306, 340 and 380 m $\mu$  in the ultraviolet (see Experimental) which were not investigated further.

(d) The complete structure of lycoclavine.

Since both the relative (see above) and absolute (73,74) stereochemistry of lycopodine is known, the results above show that lycoclavine can, in fact, be represented by LXIII, the only remaining points to be determined being the relative positions of the hydroxyl and acetoxyl groups and the stereochemistry at C-4, C-5 and C-6. In order to simplify the discussion the hydrogen at C-4 will be placed trans to the C-7, C-13 bridge, as in lycopodine. That this is indeed the correct assignment at C-4 will be demonstrated later.

The possible structures of the alkaloid can thus be illustrated with structures LXV to LXVIII.





LXV

LXVI

LXVII

LXVIII

On the basis of the NMR data presented earlier structure LXV ( $R=Ac$ ,  $R'=H$ ) was first favored for lycoclavine, since in this structure the axial proton at C-5 is flanked by an axial proton on C-4, which could lead to the observed splitting ( $\bar{ca}$  7 c.p.s.), whereas the equatorial proton on C-6 is flanked by gauche protons on C-5 and C-7 and might be expected to be weakly coupled, resulting in the broadened singlet (half-height width about 3.5 c.p.s.) actually observed (75).

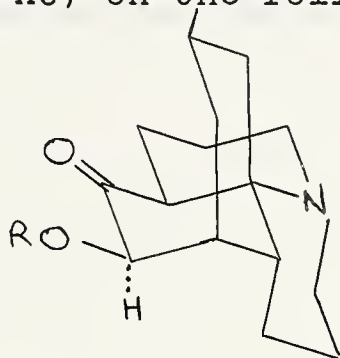
Several facts, however, were not in agreement with this formulation. Thus, although lycoclavine showed weak intramolecular hydrogen bonding in the infrared, the corresponding diol, desacetyl-lycoclavine, showed a single hydroxyl stretching vibration at  $3620\text{ cm}^{-1}$ . The diol was also resistant to oxidation with periodic acid. Both these facts speak against a cis relationship between the two groups. Furthermore, hydrolysis of acetyllycoclavine with refluxing 10% aqueous hydrochloric acid for one and a half hours gave lycoclavine in better than 90% yield. If LXV ( $R=R'=Ac$ ) were indeed the correct formulation of the diacetate the retention of the relatively unhindered equatorial acetoxyl at C-5 while the hindered axial acetoxyl at C-6 was hydrolyzed would not be expected.





Structure LXVI would also be expected to lead to a diol which would show intramolecular hydrogen bonding and react with periodic acid. Since it was felt that the oxygenated ring might be considerably distorted from the chair form (see below) structures LXVII and LXVIII remained for consideration.

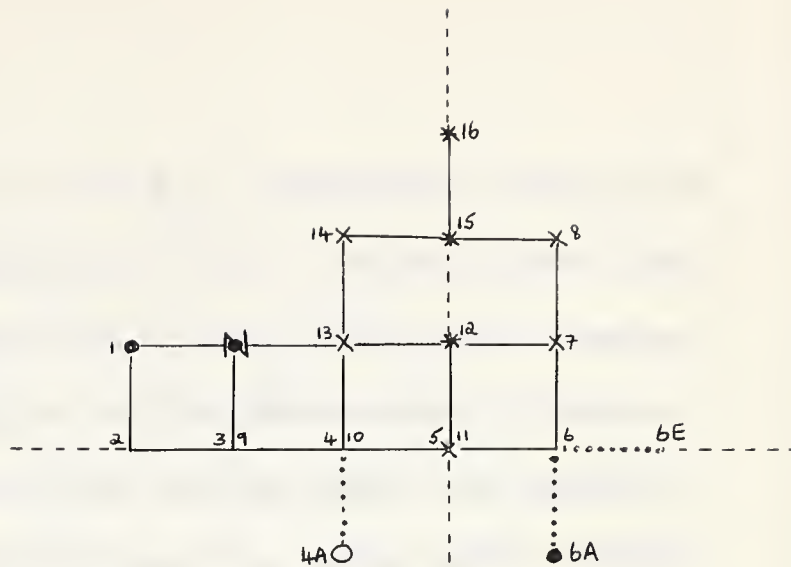
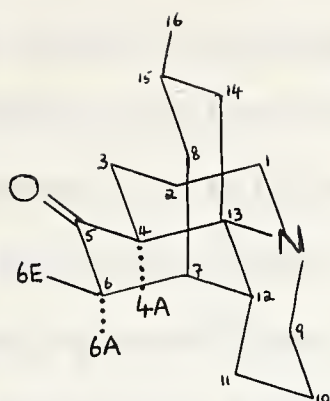
The position of the acetoxyl group was determined in the following manner. Lycoclavinone, mentioned above, could be assigned structure LXIX (R=Ac) on the following basis.



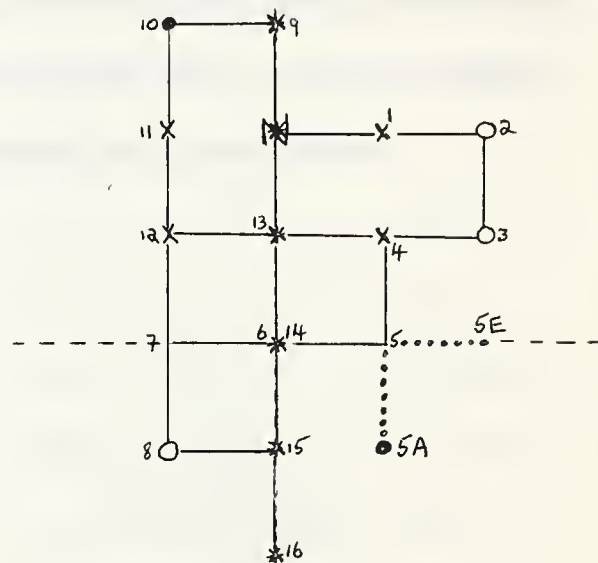
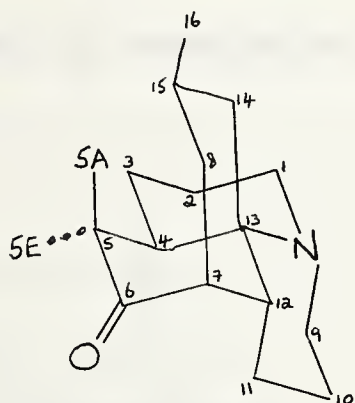
LXIX

The optical rotatory dispersion curve showed a positive Cotton effect, with extrema at  $308\text{ m}\mu$  and  $271\text{ m}\mu$  and an amplitude of  $23,000^\circ$ . Lycopodine (LXIX, OR replaced by H) under the same conditions also showed a positive Cotton effect with extrema at  $306\text{ m}\mu$  and  $271\text{ m}\mu$ , amplitude  $17,000^\circ$ . The octant rule (76) predicts a positive Cotton effect if the keto group is at C-5 (as in LXIX) and a negative Cotton effect if it is at C-6 (as in LXX). The octant diagrams for the C-5 and C-6 ketones are illustrated below, in LXXI and LXXII respectively.





LXXI



LXXII

In the octant diagrams LXXI and LXXII the symbolism of Djerassi and Klyne (91) is used. According to this scheme the following symbols are used in the above diagrams:

- × :- Atoms symmetrically disposed, contributions cancel out.
- :- Atom in back octant with positive contribution.
- o :- Atom in back octant with negative contribution.
- \* :- Atom in vertical xy plane with no contribution.

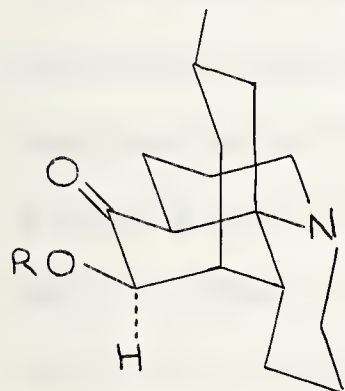
The unmarked atoms (eg. C-7 in LXXII) are in the horizontal plane and make no contribution.

The equatorial nature of the acetoxyl group is indicated both by the position of the extrema in the optical rotatory dispersion

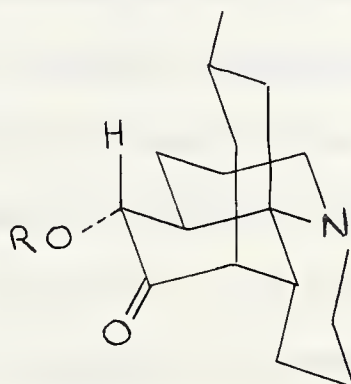




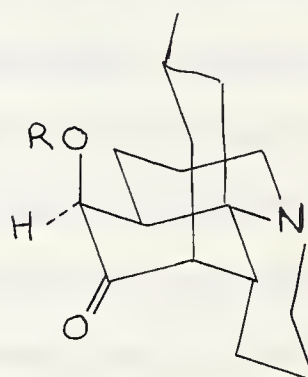
spectrum (77) and by the position (282  $m\mu$ , lycopodine 285  $m\mu$ ) of the ketonic maximum in the ultraviolet (78). The fact that the  $\alpha$ -ketol obtained by acid hydrolysis of lycoclavinone was reconverted by acetic anhydride-pyridine to the same acetoxy ketone is also consistent with structure LXIX since under the equilibrating conditions used in the hydrolysis the ketol LXIX (R=H) in which the serious non-bonded interaction between C-5 and C-15 is minimized should be favored over ketol LXX (R=H).. The fact that the hydroxyl group in the ketol is intramolecularly hydrogen bonded (concentration-independent band at 3500  $cm^{-1}$  in the infrared) is consistent with the assigned equatorial position.



LXIX



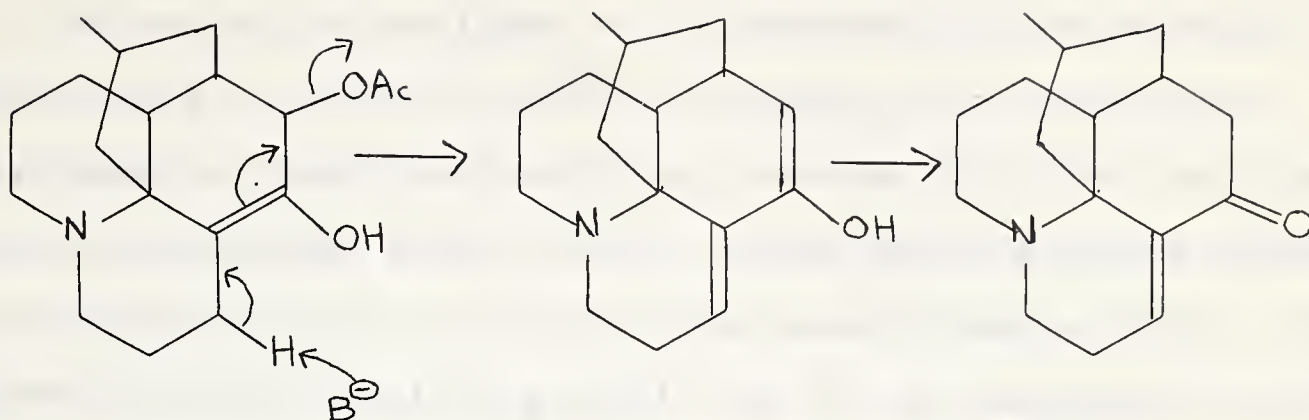
LXX



LXXIII

Pyrolysis of lycoclavinone (LXIX, R=Ac) at 240° for eight minutes led to a good yield of the  $\alpha,\beta$ -unsaturated ketone LXXIV which has also been prepared from lycopodine (see below). This facile elimination of acetic acid presumably proceeds via the enol form of the ketone, as formulated below, with the reacting material acting as its own base.





LXXIV

It was now important to determine whether lycoclavinone (LXIX, R=Ac) which is presumably the thermodynamically most stable of the four possible C-5, C-6 acetoxy ketones was actually the first product in the oxidation of lycoclavine. It was found that if the acetic acid oxidation solution was first diluted with chloroform and then ice-cold ammonium hydroxide solution added, evaporation of the chloroform extract and crystallization from n-hexane gave, instead of lycoclavinone, the  $\alpha$ -acetoxy ketone LXXIII (R=Ac), m.p. 115-118°. If the solution was first made basic by addition of ammonium hydroxide then extracted with chloroform and filtered rapidly through a short column of alumina the ketone LXX (R=Ac), m.p. 143°, was obtained.

Both LXX (R=Ac) and LXXIII (R=Ac) were isomerized to LXIX (R=Ac) when adsorbed on basic alumina for any extended length of time. After a shorter time LXXIII gave a mixture of LXX and LXIX. Similar isomerizations of steroidal  $\alpha$ -acetoxy ketones have been reported (79).

Acid hydrolysis of the 5 $\alpha$ -acetoxy-6-ketone LXX (R=Ac) gave the 6 $\alpha$ -hydroxy-5-ketone LXIX (R=H) supporting our earlier conclusion that LXIX (R=H) is the most stable of the four possible

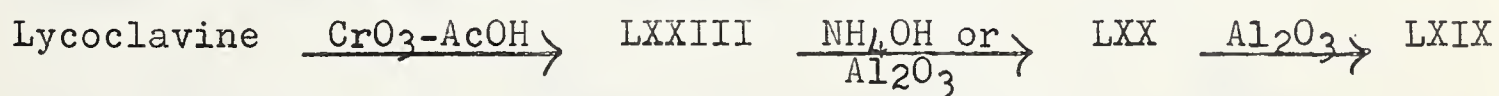




ketols.

The structures assigned to the acetoxy ketones above are based mainly on optical rotatory dispersion and ultraviolet measurements. Both the 5 $\alpha$ -acetoxy-6-ketone LXX (R=Ac) and the 5 $\beta$ -acetoxy-6-ketone LXXIII (R=Ac) showed negative Cotton effects, as predicted by the octant rule (see octant diagram LXXII). The extrema for LXX (R=Ac) were at 312 and 280 m $\mu$  (amplitude -2,300°) and for LXXIII (R=Ac) at 334 and 297 m $\mu$  (amplitude -11,300°) indicative (77) of equatorial and axial  $\alpha$ -acetoxy groups respectively. The ultraviolet maxima were at 286 m $\mu$  for LXX (R=Ac) and at 308 m $\mu$  for LXXIII (R=Ac). According to the octant diagram LXXII, the equatorial acetate LXX (R=Ac), should show a greater amplitude in the optical rotatory dispersion curve than LXXIII (R=Ac), the epimeric 5 $\beta$  (axial) acetate. The 5 $\beta$ -substituent is located in the lower right (positive) quadrant, which, although not affecting the negative sign of the amplitude should decrease the amplitude. The fact that the reverse is true no doubt reflects the distortion of the ketone-containing ring from an ideal chair (see below). Similar observations have been made with  $\alpha$ -acetoxy-11- and -12-keto steroids (80).

The oxidation of lycoclavine can now be represented by the following scheme:



The acetoxyl group in lycoclavine is, therefore, located on C-5, cis to the C-7,C-13 bridge, in agreement with structure LXVII (R=Ac, R'=H) but not with structure LXVIII.

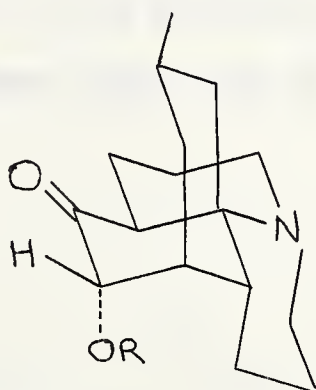
Further evidence for the diaxial orientation of the substituents at C-5 and C-6 and for the configuration at C-4 was



obtained by a study of the reduction products obtained from the various isomeric  $\alpha$ -ketols and  $\alpha$ -acetoxy ketones now available to us.

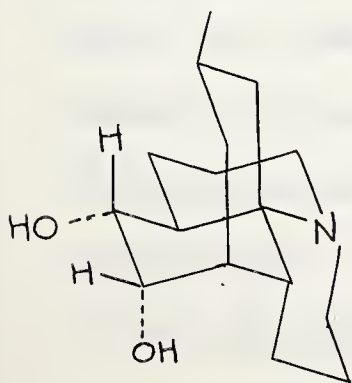
It has been shown above that lithium aluminum hydride reduction of lycopodine gives the axial alcohol, dihydrolycopodine XXIX, whereas dissolving metal reduction gives the epimeric equatorial alcohol,  $\alpha$ -dihydrolycopodine XXX.

Alkaloid L.20 whose constitution and stereochemistry will be shown later to be identical to that depicted in structure LXXV (R=H) was reduced under similar conditions.

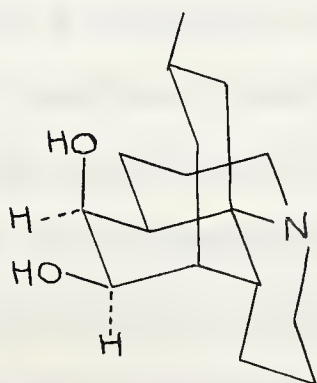


LXXV

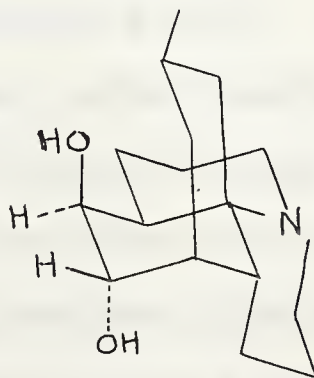
Reduction with lithium aluminum hydride in ether gave the diol LXXVIII, identical in all respects to desacetyllycoclavine. The structure LXXVIII was assigned on the assumption that the approach of the reducing agent would be on the side opposite to the C-7,C-13 bridge, as in the case of lycopodine.



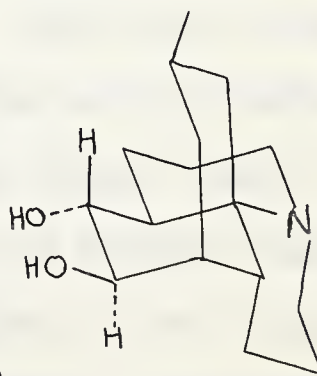
LXXVI



LXXVII



LXXVIII

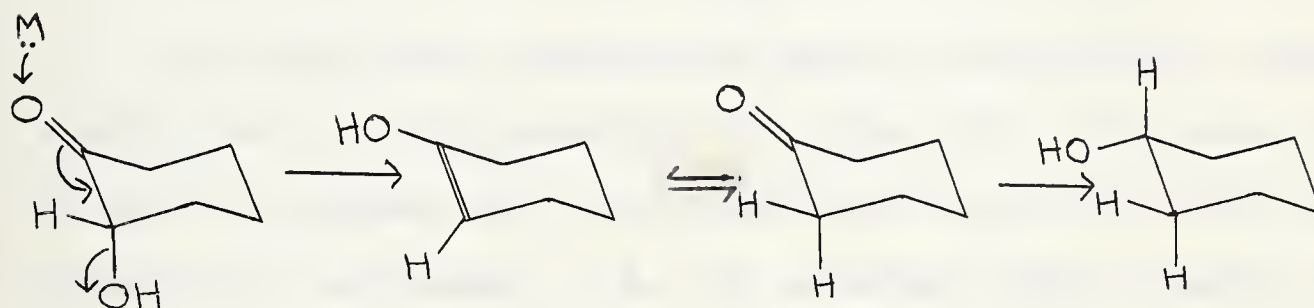


LXXIX





This assumption is supported by the results obtained on reduction of the ketones LXIX and LXX. Reduction of 6 $\beta$ -hydroxylycopodine LXIX (R=H) with lithium aluminum hydride gave a new diol, m.p. 230-231°, assigned structure LXXVII on the basis of its mode of formation. Lithium-ammonia-methanol reduction of the ketol LXIX (R=H) yielded a third diol, m.p. 209-210°, assigned the diequatorial structure LXXIX again on the basis of its mode of formation. Attempts to prepare the fourth diol LXXVI by dissolving metal reduction of alkaloid L.20 were unsuccessful, leading only to reductive removal of the C-6 hydroxyl group and formation of  $\alpha$ -dihydrolycopodine XXX. The elimination of the  $\alpha$ -group is typical of  $\alpha$ -axial hydroxy ketones (81) and is illustrated in the sequence LXXX  $\longrightarrow$  LXXXI.



LXXX

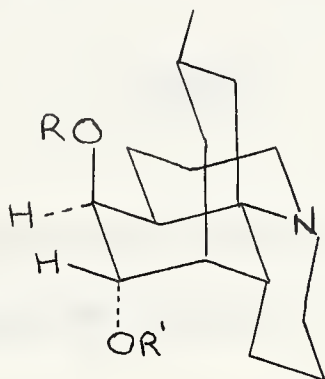
LXXXI

Reduction of the 5 $\alpha$ -acetoxy-6-ketone LXX with lithium aluminum hydride led to a diol m.p. 234-235°, differing from the other three and therefore assigned structure LXXVI. All four diols showed different infrared spectra, single spots on thin layer chromatography and depression of mixed melting points where appropriate. It is interesting to note that the hydride reduction of the 5 $\alpha$ -acetoxy-6-ketone LXX involves approach of the reducing species from the same side as the C-7,C-13 bridge. Presumably,



in this case, approach to the opposite side is hindered by the C-12 methylene group.

Since each of the diols LXXVI, LXXVII and LXXIX must have at least one equatorial hydroxyl group, the product from the hydride reduction of alkaloid L.20 which is identical to desacetyllycoclavine is, in fact, the diaxial diol LXXVIII and lycoclavine itself is LXVII (R=Ac, R'=H).

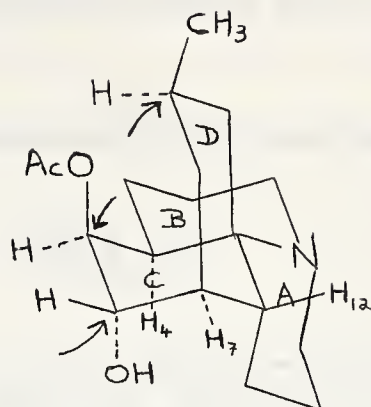


LXVII

As noted above, lycoclavine shows intramolecular hydrogen bonding but the corresponding diol does not. To account for this it must be assumed that the oxygenated ring is severely distorted towards the half-chair, i.e. the dihedral angle between the two groups must approach  $120^\circ$ . It is known, for instance, that trans cyclo-1:2-pentanediol does not show intramolecular hydrogen bonding, but that the corresponding monoacetyl derivative does (82). Measurements on Dreiding models indicate an internuclear distance of  $\overline{\text{ca}} 1 \text{ \AA}$  between the C-5 oxygen and the C-15 hydrogen in lycoclavine. The sum of the van der Waals radii is  $2.6 \text{ \AA}$  so that a distortion of ring C (and presumably also ring D) is to be expected. The direction of this distortion is indicated in structure LXXXII, a stereochemical representation of lycoclavine.







LXXXII

A more quantitative estimation of this distortion can be obtained by a consideration of the NMR spectra of some of the compounds mentioned earlier.



(e) Nuclear Magnetic Resonance data for lycoclavine and related compounds.

The peaks under consideration are tabulated in Table IV.

TABLE IV

COMPOUND	CHEMICAL SHIFTS* (SPLITTING)**			
	C-5	C-6	-OCOCH <sub>3</sub>	C-16
Lycoclavine LXXXII	5.11 (6.9)	6.40 (3.3)	7.93	9.09 (6.0)
Acetyllycoclavine	4.92 (6.8)	5.32 (3.2) <sup>##</sup>	7.92, 7.93	9.08 (6.0)
Lycoclavinone LXIX (R=Ac)		4.60 (5.5)	7.83	9.17 (5.5)
5 $\alpha$ -acetoxy-6-ketone LXX (R=Ac)	4.73 (11.5)		7.83	8.96 (5.8)
5 $\beta$ -acetoxy-6-ketone LXXIII (R=Ac)	4.61 (9.0)		7.89	9.03 (6.0)
Acetyl L.20 LXXV (R=Ac)		5.11 (3.5)	7.94	9.16 (4.5)
Lycopodine				9.14 (5.0)
"Lycopodane" XXXI				9.13 (6.0)
Dihydrolycopodine acetate XXXIII	4.90 <sup>##</sup>		7.96	9.08 (6.0)
$\alpha$ -dihydrolycopodine acetate XXXII	4.98 <sup>##</sup>		7.95	9.09 (5.7)
Anhydrodihydro- lycopodine XXXV				9.04 (5.5)

\*  $\tau$ -values

\*\* in c.p.s.

# width at half height

## center of multiplet

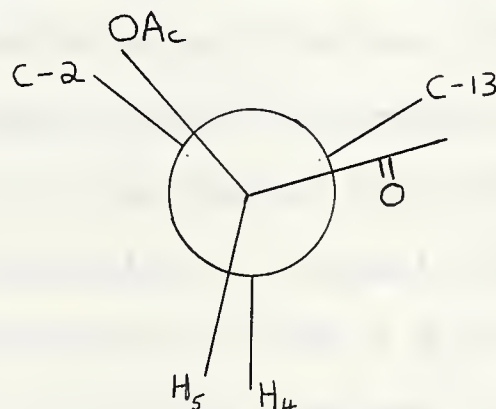




It is well known (75) that the coupling constant between vicinal hydrogens is related to their dihedral angle. In the particular case of  $\alpha$ -acetoxycyclohexanones in fused ring systems, the following relationships have been found (83) to apply:

$$J_{HH'} \begin{cases} 10 \cos^2 \phi & 0^\circ \leq \phi \leq 90^\circ \\ 16 \cos^2 \phi & 90^\circ \leq \phi \leq 180^\circ \end{cases}$$

In the  $5\beta$ -acetoxy-6-ketone LXXIII the coupling constant between the protons on C-4 and C-5 ( $J_{45}$ ) is 9 c.p.s. (see Table IV). Using the Johnson expression given above this indicates a dihedral angle of  $18^\circ$ , indicating a considerable distortion from the normal  $60^\circ$ . This is illustrated in the Newman projection LXXXIII.



LXXXIII

The  $5\alpha$ -acetoxy-6-ketone LXX shows a similar distortion ( $J_{45}=11.5$  c.p.s.,  $\phi=142^\circ$  instead of  $180^\circ$ ). In the C-5 ketone lycoclavinone (LXIX, R=Ac) where the C-5,C-15 interaction is minimized because of the trigonal nature of C-5 the calculated angle is  $42^\circ$  ( $J_{67}=5.5$  c.p.s.).

The acetyl derivative of L.20 (LXXV, R=Ac) gave a broadened singlet (width at half-height about 3.5 c.p.s.) indicative of an



angle of about  $60^\circ$  between  $H_6$  and  $H_7$ . Thus it appears that in the C-6 ketone series the non-bonded interaction between C-5 and C-15 is relieved, at least in part, by a distortion of ring C from an ideal chair towards the half chair. This strain could also be relieved if ring D assumed the boat form, but as has been pointed out previously (66) this introduces a serious bowsprit-flagpole interaction between C-12 and C-16. The NMR data obtained with the C-5 ketones indicates a similar, but smaller, distortion of ring C in this series. Such a flattening of the C ring would increase the angle between the C-4 and C-6 and account for the unusually low ( $1700\text{ cm}^{-1}$ ) (44) carbonyl stretching frequency of lycopodine (84).

The NMR spectra of lycoclavine and its acetyl derivative (see Table IV) are in good agreement with the proposed structures if we make the reasonable assumption that ring C is distorted to at least the same extent as the C-6 ketones. Applying the Karplus-Conroy correlation (75) (The Johnson expression applies only to six-membered rings containing a trigonal carbon atom adjacent to the bonds under consideration.) (83) a  $H_4-C-C-H_5$  dihedral angle of  $20^\circ$  would lead to a coupling constant  $J_{45}$  of 7 c.p.s. (observed 6.8 and 6.9).  $J_{56}$  and  $J_{67}$  would be expected to be small (both angles approach  $90-100^\circ$  in the distorted chair) explaining the fact that C- $H_5$  is not further split and C- $H_6$  is a somewhat broadened singlet.

Inspection of Table IV suggests a possible relationship between the chemical shift of the C-16 methyl group and the presence or absence of a carbonyl group at C-5. Thus those compounds with a C-5 keto group show the C-methyl group resonance at  $9.14-9.17\tau$



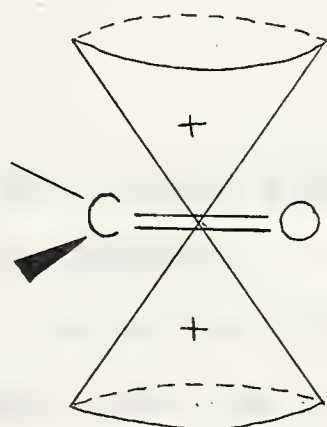


while, with two exceptions, those compounds without a carbonyl group in ring C show this absorption at 9.08-9.09 $\tau$ . The exceptions are dihydrodeoxylycopodine XXXI ("lycopodane") which has the C-methyl doublet centered at 9.13 $\tau$  and anhydrodihydrolycopodine XXXV with the doublet at 9.04 $\tau$ .

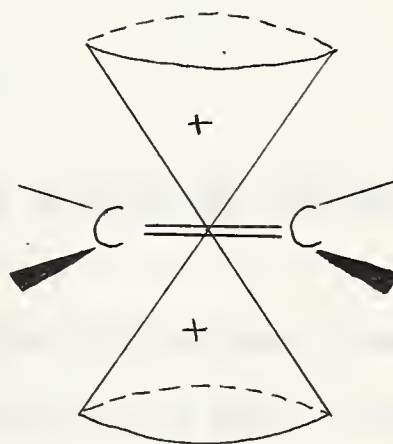
The differences noted are possibly due to the long range shielding effects of the carbonyl group and olefinic double bond (85). Inspection of models reveals that in the C-6 ketones the C-methyl group no longer lies in the shielding region of the carbonyl and may in fact be deshielded by it. In agreement with this view, the two C-6 ketones absorb at 8.96 $\tau$  and 9.03 $\tau$ . In the  $\Delta^{4,5}$  olefin XXXV the C-methyl group is probably deshielded by the olefinic double bond.

These effects are illustrated in structures LXXXIV to LXXXVIII.

Shielding cones due to carbonyl group and olefinic linkage.



LXXXIV

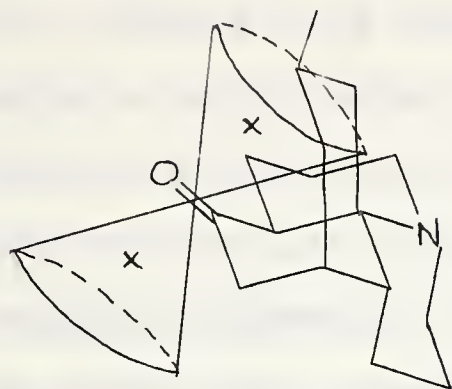


LXXXV

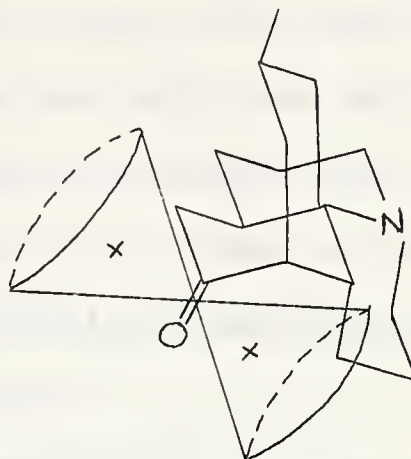
N.B. Deshielding occurs outside the cones.



Shielding cones due to the carbonyl group in C-5 and C-6 ketones.

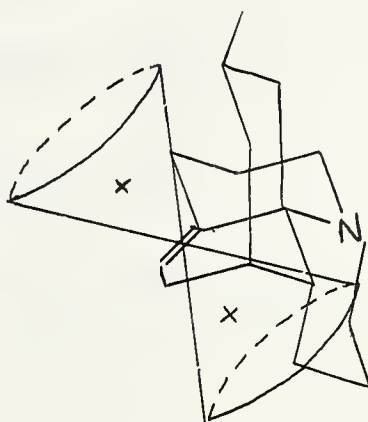


LXXXVI



LXXXVII

Shielding cone due to the olefinic linkage in XXXV.



LXXXVIII

(f) The optical rotatory dispersion curves of the distorted compounds.

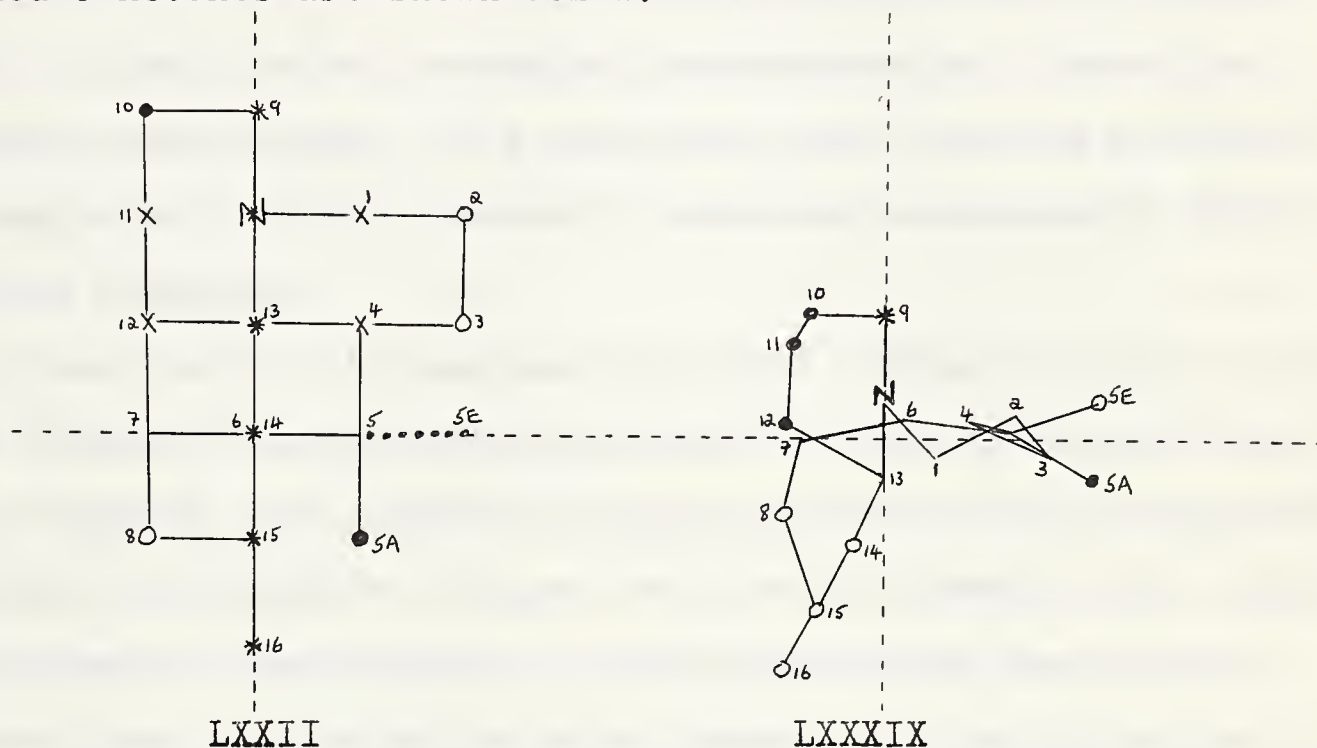
The octant diagram LXXII for the C-6 ketone (see above) assumed that the oxygenated ring was in the chair form. It will now be demonstrated that the distortion of the oxygenated (and bridge) rings does not affect the prediction that the C-6 ketones would show a negative Cotton effect.

Dreiding models show that in the deformed compound (with the  $4\alpha - 5\alpha$  dihedral angle  $20^\circ$ , instead of the usual  $60^\circ$ ) the nitrogen



atom, as well as the C-1, C-2, C-3, C-4, C-12 and C-13 atoms are in, or very close to, the horizontal plane, made by C-5, C-6 and C-7. Since C-9 is in the vertical plane, the only carbon atoms making a contribution to the sign and amplitude of the Cotton effect are C-10 and C-11 (located in the upper left (positive) quadrant) and C-8, C-14, C-15 and C-16 (found in the lower left (negative) quadrant). The 5-equatorial substituent now lies in the upper right (negative) quadrant.

The octant diagrams LXXII and LXXXIX for the undeformed and deformed 6-ketones are shown below.



The octant diagram LXXXIX indicates that the sign of the Cotton effect in the deformed compounds will be negative. The relative amplitudes of the 5-equatorial (designated 5E) and 5-axial (5A) acetates is clearly difficult to predict, since the distortion in the oxygenated and bridge rings will be different in the two compounds.

In view of the fact that acetyllycoclavine is hydrolyzed by hot dilute mineral acid to lycoclavine, the possibility arose that





the lycoclavine isolated was actually formed during the isolation process. Although this possibility cannot be completely excluded, it seems unlikely, since lycoclavine can also be isolated in good yield by percolation of the ground plant with cold dilute acetic acid and immediate extraction of the alkaloids into chloroform.

#### V. THE 6-BROMOLYCOPODINES AND THEIR REACTIONS.

It has already been mentioned that bromination of lycopodine with an equimolar quantity of bromine in either carbon tetrachloride or chloroform gives rise to a crystalline product which appeared to be a 1:1 mixture of lycopodine hydrobromide and a monobromolycopodine hydrobromide. The analytical data reported by MacLean (42) suggested that their material contained approximately 80% of the bromo compound.

It was found that repeated fractional crystallization of the mother liquors from the crystallization of the 1:1 mixture above gave a compound, m.p. 266-269°, which appeared to be pure monobromolycopodine hydrobromide. Since the latter is somewhat more soluble than lycopodine hydrobromide in the solvents used the material obtained from the bromination after several recrystallizations is actually richer in the non-brominated material, explaining the variation in analytical data between our results and those reported earlier (42).

Co-crystallization of lycopodine hydrobromide and the pure monobromolycopodine hydrobromide from a small volume of solvent yielded material the melting point and infrared spectrum of which were similar to those of our recrystallized bromination product.

The fact that all the bromine (1 equivalent) had been consumed



in our case prompted a further study of this reaction.

It was found that one half equivalent of bromine was rapidly decolorized on addition to a solution of one equivalent of lycopodine in chloroform. Evaporation of the solvent and crystallization of the residue from methanol-acetone gave lycopodine hydrobromide in 60% yield. The colorless mother liquors rapidly darkened to give a brown gum. Essentially the same result was obtained when carbon tetrachloride was used as solvent.

These results could be attributed either to competitive oxidative attack at the tertiary nitrogen or to attack by lycopodine, acting as a base, on the initially formed bromolycopodine yielding hydrogen bromide and the  $\alpha,\beta$ -unsaturated ketone LXXIV. The second possibility, however, would not readily explain the formation of more than 50% of lycopodine hydrobromide from one half equivalent of bromine. This possibility was excluded when it was found that lycopodine and monobromolycopodine hydrobromide on admixture in chloroform did not give the unsaturated compound LXXIV. Instead, salt exchange occurred to give lycopodine hydrobromide and monobromolycopodine, presumably either because the former is less soluble than bromolycopodine hydrobromide in the solvents used (which agrees with our earlier conclusions) or because lycopodine is the stronger of the two bases.

The results obtained from the bromination must, therefore, be attributed to competitive oxidative attack of bromine at the tertiary nitrogen. In confirmation of this it was found that both dihydrolycopodine XXIX and O-acetyldihydrolycopodine XXXIII gave approximately 75% yields of their hydrobromides on treatment with one half equivalent of bromine (which was decolorized immediately)



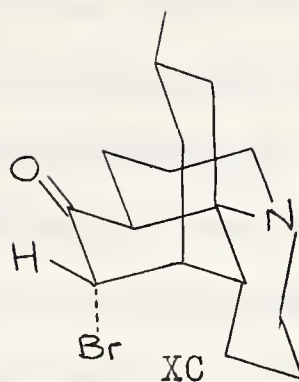
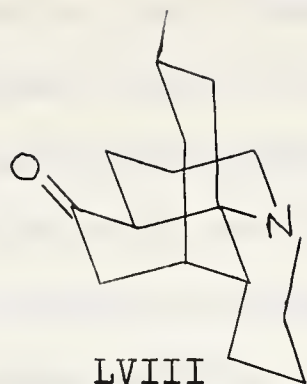


in chloroform. The hydrobromides of XXIX and XXXIII did not decolorize even a trace of bromine under similar conditions.

In confirmation of the above, bromination of lycopodine hydrobromide in chloroform using one equivalent of bromine and a slight excess of hydrogen bromide gave, in better than 90% yield, 6 $\alpha$ -bromolycopodine hydrobromide XC.HBr. The position and orientation of the bromine was shown in the following way. The nuclear magnetic resonance spectrum of XC showed a one-proton signal at 5.82 $\tau$ , (broadened singlet). Since this signal is attributed to the proton on the carbon carrying the bromine, then bromination must have occurred at C-6 rather than at C-4. The infrared spectrum of the hydrobromide in chloroform solution showed carbonyl absorption at 1711  $\text{cm}^{-1}$  little shifted from that of lycopodine hydrobromide (1707  $\text{cm}^{-1}$ ) and indicative of the axial nature of the C-6 bromine (86). The ultraviolet spectrum of the bromo compound ( $\lambda_{\text{max}}$  306  $\text{m}\mu$ ) showed the expected (87) bathochromic shift relative to lycopodine hydrobromide ( $\lambda_{\text{max}}$  280  $\text{m}\mu$ ).

With the structure of the bromo compound thus assigned, it was of interest to examine its optical rotatory dispersion curve in the light of the axial haloketone rule (88) and provide further evidence for the absolute configuration of lycopodine. The absolute configuration of lycopodine, represented by structure LVIII, was first assigned by application of the octant rule to lycopodine itself (74).





If structure XC represents the absolute configuration of 6 $\alpha$ -bromolycopodine the axial haloketone rule predicts that it will show a positive Cotton effect whereas the enantiomer will show a negative Cotton effect. The octant diagram LXXI for the ketone with the absolute configuration LVIII has already been discussed. In fact, 6 $\alpha$ -bromolycopodine hydrobromide does exhibit a positive Cotton effect with extrema at 332 and 280 m $\mu$ , amplitude +10,650°. Lycopodine itself shows a positive Cotton effect (74), amplitude +17,000°. The octant diagram LXXI suggests that the 6 $\alpha$ -bromo compound should have a greater amplitude than lycopodine since in the former the bromine atom would be in the lower right hand quadrant (a positive quadrant) if the absolute configuration of the 6 $\alpha$ -bromo compound is, in fact, that represented by XC. This apparent anomaly was cleared up when it was found that lycopodine hydrobromide exhibits a negative Cotton effect, with extrema at 305 and 268 m $\mu$ , amplitude -2,770°. It would appear, therefore, that the positively charged nitrogen which in the octant diagram LXXI appears in the rear upper left octant has like fluorine (76) a negative specific rotativity. An alternative explanation that the difference is due to a change in conformation on salt formation appears unlikely on the basis of examination of Dreiding models. Similar changes in the sign of the





Cotton effect on salt formation have been observed in the diterpene alkaloid series (74a). In agreement with these conclusions both lycopodine perchlorate and lycopodine methiodide show negative Cotton effects, with amplitudes similar to that of lycopodine hydrobromide. A solution of lycopodine in acetic acid also shows a negative Cotton effect. In agreement with the octant rule (76) the free base 6 $\alpha$ -bromolycopodine XC shows a more positive Cotton effect (amplitude +29,500°) than does lycopodine.

These results are tabulated in Table V and are in agreement with the originally deduced (74) absolute configuration.

TABLE V

Optical Rotatory Dispersion data for lycopodine, lycopodine salts and the 6-bromolycopodines.<sup>\*#</sup>

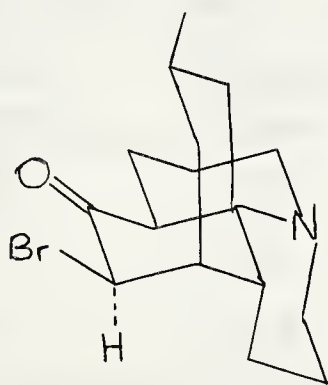
Compound	First Extremum		Second Extremum		Amplitude °
	$\lambda_{m\mu}$	$[\phi]^\circ$	$\lambda_{m\mu}$	$[\phi]^\circ$	
Lycopodine	304	+3,650	265	-13,400	+17,050
Lycopodine perchlorate	302	-1,600	260	+ 280	- 1,880
Lycopodine methiodide	304	-2,450	268	+ 250	- 2,700
Lycopodine in AcOH	300	-2,270	263	+ 540	- 2,810
Lycopodine hydrobromide	305	-2,340	268	+ 430	- 2,770
6 $\alpha$ -Bromolycopodine hydrobromide	332	+4,550	280	-6,100	+10,650
6 $\beta$ -Bromolycopodine hydrobromide	350	- 870	315	-1,015	-----
6 $\alpha$ -Bromolycopodine	335	+8,950	294	-20,550	+29,500

\* in 0.5 dm. cell

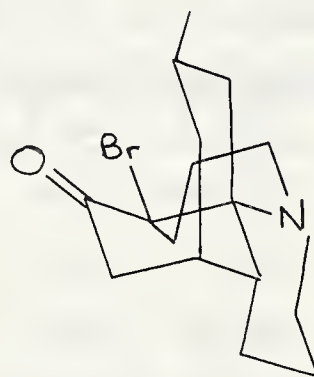
# methanol solvent unless otherwise stated



When a solution of 6 $\alpha$ -bromolycopodine hydrobromide XC.HBr in glacial acetic acid was heated on the steam bath for one hour the product, isolated in 75% yield after evaporation of the acetic acid and washing of the residue with acetone, showed carbonyl absorption (nujol) of approximately equal intensity at 1720 and 1703  $\text{cm}^{-1}$ . By fractional crystallization from methanol it was possible to isolate the component responsible for the 1720  $\text{cm}^{-1}$  in about 10% overall yield. This has been assigned the structure 6 $\beta$ -bromolycopodine hydrobromide XCI.HBr on the basis of its analysis and its infrared (maximum at 1728  $\text{cm}^{-1}$  in chloroform) and ultraviolet ( $\lambda_{\text{max}}$  276  $\text{m}\mu$ ) spectra, both of which are indicative of an equatorial  $\alpha$ -bromo ketone (86,87). The alternative formulation, 4 $\beta$ -bromolycopodine hydrobromide, although not excluded by this data, is considered highly unlikely since it would force the molecule to adopt a conformation in which ring B is in a boat conformation, involving a serious bowsprit-flagpole interaction. This is illustrated in structure XCII.



XCI



XCII

The negative optical rotatory dispersion curve of XCI.HBr is almost plain with a slight inflexion toward the negative side at 310  $\text{m}\mu$ . Attempts to effect the epimerization XC.  $\longrightarrow$  XCI in higher yield by the use of more strenuous reaction conditions resulted in





extensive decomposition and much lower overall yields. When 6 $\beta$ -bromolycopodine hydrobromide was subjected to the epimerizing conditions noted above the crude product did not show a detectable (by infrared) amount of the 6 $\alpha$ -epimer demonstrating that the product obtained from the 6 $\alpha$ -compound is not an equilibrium mixture.

The free bromo ketone XC which, in agreement with assigned structure, showed an ultraviolet maximum at 305 m $\mu$  (log  $\epsilon$ =2.22) was extremely sensitive to base. It was prepared by shaking a chloroform solution of the hydrobromide with cold dilute ammonium hydroxide or sodium bicarbonate. It decomposed on melting with the elimination of hydrogen bromide and the formation of the  $\alpha,\beta$ -unsaturated ketone LXXIV (see below) or on standing in methanol as revealed by the decrease in the amplitude of the optical rotatory dispersion curve (see Table VI) and by the appearance of salt bands (+NH) in the infrared and an ultraviolet maximum at 243 m $\mu$  in material recovered from the ORD measurements.

TABLE VI

Variation with time of the ORD amplitude of 6 -bromolycopodine XC.

Time (minutes)	First Extremum		Second Extremum		Amplitude °
	$\lambda_{m\mu}$	$[\phi]^\circ$	$\lambda_{m\mu}$	$[\phi]^\circ$	
12	335	+8,950	294	-20,550	+29,400
170	337	+8,530	294	-18,740	+26,270
1,450	335	+4,055	287	- 9,875	+13,930

Treatment of 6 $\alpha$ -bromolycopodine hydrobromide XC.HBr with aqueous sodium hydroxide at room temperature yielded a mixture of the enolic  $\alpha$ -diketone LXIV and the unsaturated ketone LXXIV. The diketone LXIV is presumably formed by aerial oxidation of the  $\Delta^5$ -enolate form of the corresponding  $\alpha$ -ketol (72) and the un-



saturated ketone LXXIV by 1:4 elimination of hydrogen bromide from the  $\Delta^4$ -enolate form of the bromoketone (this type of elimination has already been discussed).

The structure of the  $\alpha,\beta$ -unsaturated ketone LXXIV was shown in the following way. The ultraviolet spectrum showed a maximum at  $244\text{ m}\mu$  ( $\log \epsilon = 3.9$ ). (The calculated value for structure LXXIV is  $242\text{ m}\mu$  (92)). The infrared spectrum showed peaks of almost equal intensity at  $1680$  and  $1610\text{ cm}^{-1}$  indicating (89) the cisoid nature of the  $\alpha,\beta$ -unsaturated ketonic function. The NMR spectrum revealed the presence of a single olefinic proton (poorly resolved triplet at  $3.04\tau$ ) located at the  $\beta$ -position of the unsaturated system (90). Finally, reduction of the unsaturated ketone LXXIV with lithium in liquid ammonia gave lycopodine showing that no skeletal rearrangement had occurred during the dehydrobromination. The ketone LXXIV has recently been prepared from flabelliformine which was shown to be  $4\alpha$ -hydroxylycopodine (45), as well as from lycoclavine (see above).

When sodium bicarbonate was substituted for sodium hydroxide in the hydrolysis of  $6\alpha$ -bromolycopodine hydrobromide a crystalline compound,  $\text{C}_{16}\text{H}_{25}\text{O}_2\text{N}$ , m.p.  $258-259^\circ$ , was obtained in high yield. The high melting point and the infrared spectrum which showed (in nujol) an unusually broad OH stretching vibration ( $2400-3200\text{ cm}^{-1}$ ) were reminiscent of alkaloid L.20, first isolated by Manske and Marion from Lycopodium ludidulum Michx. (8) and which was concurrently under study in these laboratories (26). Direct comparison (mixed melting point, infrared spectrum, optical rotatory dispersion curves) confirmed the identity of the two compounds. This finding, coupled with the evidence presented below, necessitates





a revision of the molecular formula of alkaloid L.20 from  $C_{17}H_{27}O_2N$  (8) to  $C_{16}H_{25}O_2N$ .

The infrared spectrum of alkaloid L.20 in alcohol-free chloroform showed absorption at  $3620\text{ cm}^{-1}$  (non-hydrogen bonded hydroxyl) and  $1710\text{ cm}^{-1}$  (ketone), thus defining the nature of the two oxygen atoms. The ultraviolet spectrum of the alkaloid showed a maximum at  $296\text{ m}\mu$  ( $\log \epsilon = 1.85$ ). Lycopodine absorbs in the ultraviolet at  $285\text{ m}\mu$ . The bathochromic shift from  $285$  to  $296\text{ m}\mu$  would be expected for either  $4\alpha$ -hydroxylycopodine or  $6\alpha$ -hydroxylycopodine. (It is known (78) that the introduction of an axial hydroxyl group  $\alpha$  to a ketone causes a bathochromic shift of  $10\text{-}20\text{ m}\mu$  in the ketone  $n-\pi^*$  absorption band). It has recently been shown that flabelliformine, an alkaloid first isolated from Lycopodium flabelliforme (21) and later (see above) from Lycopodium clavatum, is  $4\alpha$ -hydroxylycopodine (45). The alternate possibility, that alkaloid L.20 is in fact  $6\alpha$ -hydroxylycopodine, was readily proven in the following manner.

The reduction of alkaloid L.20, in these laboratories (26), with calcium in liquid ammonia (81) yielded lycopodine confirming that the carbon-nitrogen skeleton of lycopodine was retained in L.20 and that the hydroxyl group in L.20 is axial and  $\alpha$  to the carbonyl group. The secondary nature of the hydroxyl group was confirmed by the observations that L.20 is transformed to a mixture of the diosphenol LXIV and the unsaturated ketone LXXIV in aqueous sodium hydroxide in the presence of air and by the fact that the NMR spectrum of the O-acetyl derivative of L.20 shows a one-proton signal at  $5.11\tau$  ( $\underline{CH}OAc$ ).

Thus alkaloid L.20 is  $6\alpha$ -hydroxylycopodine LXXV ( $R=H$ ) and the



hydrolysis of 6 $\alpha$ -bromolycopodine XC proceeds with overall retention of configuration. Direct backside attack by hydroxyl to give the 6 $\beta$ -hydroxy compound directly is extremely hindered by the C-7, C-13 bridge. The hydrolysis may therefore proceed by prior epimerization to the 6 $\beta$ -bromo compound XCI which could then suffer backside attack to give the 6 $\alpha$ -hydroxy compound L.20. This suggestion was substantiated by the observation that 6 $\beta$ -bromolycopodine hydrobromide XCI.HBr also gives a good yield of L.20 on hydrolysis with aqueous sodium bicarbonate.

It has already been reported (see above) that reduction of alkaloid L.20 with lithium aluminum hydride gives the 5,6 diaxial diol, desacetyllycoclavine LXXVIII. This sequence therefore, coupled with the fact (see above) that the diol LXXVIII yields the naturally occurring acetyllycoclavine on acetylation with acetic anhydride-pyridine and the fact that the diacetate gives lycoclavine on acid hydrolysis completes the conversion of lycopodine to the three alkaloids.

Our attention turned at this point to a study of some further reactions of alkaloid L.20 and of the bromo compounds XC and XCI.

Following the study of the epimerization of the 6 $\alpha$ -bromo ketone XC to the 6 $\beta$  epimer XCI attempts were made to convert alkaloid L.20 to the epimeric 6 $\beta$ -hydroxylycopodine LXIX (R=H) which had already been prepared from lycoclavine (see above).

L.20 was found to be stable in dilute aqueous ammonia. Treatment of the alkaloid with chloroform saturated with hydrogen chloride at room temperature or with refluxing benzene containing p-toluenesulphonic acid led to the recovery of starting material, although the infrared spectra of the crude product in both cases





indicated the presence of the  $\alpha,\beta$ -unsaturated ketone LXXIV. In fact the unsaturated ketone LXXIV was formed in better than 80% yield when L.20 was refluxed for three hours in 10% aqueous hydrochloric acid. The dehydration, which is a 1:4 elimination characteristic of 6 $\alpha$ -substituted lycopodines (compare 6 $\alpha$ -bromolycopodine above and 6 $\alpha$ -acetoxylycopodine below), presumably proceeds through the  $\Delta^4$  enolate form of L.20. The epimerization of L.20 to 6 $\beta$ -hydroxylycopodine LXIX (R=H) was readily accomplished by treatment with sodium propoxide in n-propanol in an atmosphere of nitrogen (26) or, better, by slowly passing L.20 through a column of basic alumina.

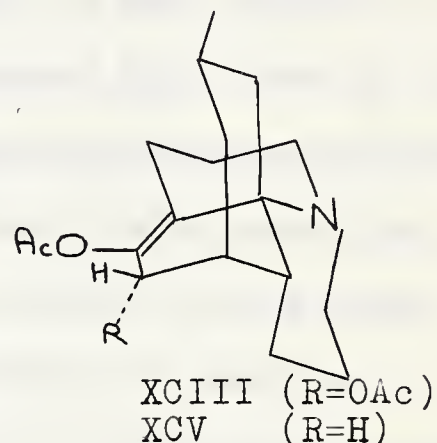
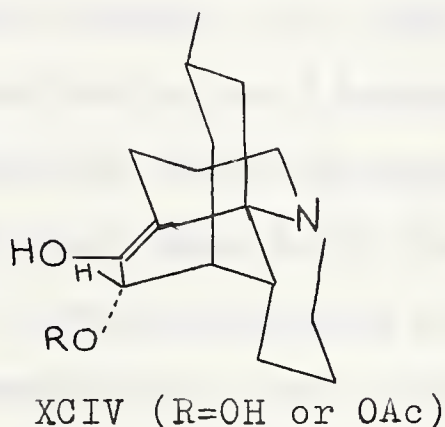
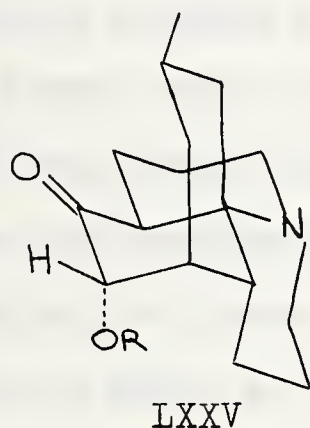
It had already been observed that the 5 $\alpha$ - and 5 $\beta$ -acetoxy-6-ketones LXX (R=Ac) and LXXVIII (R=Ac) both yielded the 6 $\beta$ -acetoxy-5-ketone LXIX (R=Ac) when passed through a column of basic alumina. The behaviour of the 6 $\alpha$ -acetoxy-5-ketone, (O-acetyl L.20), LXXV (R=Ac), under similar conditions was therefore of interest.

Acetylation of alkaloid L.20 with acetic anhydride-pyridine at room temperature did not give the expected O-acetyl L.20. Instead, a colorless oil was obtained which analyzed for C<sub>20</sub>H<sub>29</sub>O<sub>4</sub>N. This compound showed maxima in the infrared at 1768, 1741, 1688, 1238, 1223 and 1214 cm<sup>-1</sup>. The ultraviolet spectrum showed only end absorption. This data appeared to agree well with that expected for compound XCIII, that is, the enol-acetate of O-acetyl L.20. In confirmation of this assignment the NMR spectrum showed peaks at 7.98 and 8.06 $\tau$  (two acetate methyl groups), as well as a one-proton signal at 5.02 $\tau$  (CHOAc). The perchlorate of XCIII, m.p. 258-259°, exhibited infrared maxima at 1738, 1725, 1691, 1246 and 1228 cm<sup>-1</sup> (nujol). The  $\alpha,\beta$ -unsaturated ketone LXXIV was also



formed to a small extent in the acetylation, as indicated by characteristic bands in the infrared spectrum of the crude product.

It is interesting to note that under identical reaction conditions lycopodine is recovered unchanged. Thus it appears that a 6 $\alpha$ -hydroxyl or 6 $\alpha$ -acetoxyl group facilitates the enolization of the 5-keto group to the  $\Delta^4$  enol XCIV, thereby relieving some of the non-bonded interaction between the oxygen function at C-6 and the C-11 methylene group. This is indicated in the following structures.



The  $\Delta^4$  enol acetate XCV of lycopodine was prepared in high yield by refluxing lycopodine in acetic anhydride containing p-toluenesulphonic acid, the acetic anhydride being allowed to distill slowly out of the reaction flask (93). The NMR spectrum of XCV shows no olefinic protons proving that the structure assigned is correct, and gave signals at 7.86 $\tau$  (3H,  $\text{OCOCH}_3$ ) and 9.12 $\tau$  (3H,  $\text{CHCH}_3$ , doublet  $J=6$  c.p.s.). The infrared spectrum of XCV (in carbon tetrachloride) showed maxima at 1755  $\text{cm}^{-1}$  (attributed to -OAc) and 1696  $\text{cm}^{-1}$  (olefinic double bond). Provided that the direction of acid catalyzed enol-acetylation is a measure of the preferred direction of acid catalyzed enolization, this indicates that the  $\Delta^4$  enol form of lycopodine is preferred over the  $\Delta^5$  enol.





The fact that bromination occurs virtually quantitatively at C-6 (see above) must be due to the greater degree of steric hindrance at C-4 than at C-6.

Returning now to the enol acetate XCIII, it was found that hydrolysis with 10% aqueous hydrochloric acid at 100° for two hours gave a mixture of L.20 (LXXV, R=H, 61%) and the unsaturated ketone LXXIV (36%), (the latter, as seen already, can be produced from L.20 under these conditions). Since L.20 is the 6-axial hydroxy compound, this proves that the structure XCIII assigned to the enol acetate is indeed correct, i.e. that the enol acetate was not formed after epimerization to the 6 $\beta$ -compound LXIX (R=H or Ac). This had already been inferred, since 6 $\beta$ -hydroxylycopodine LXIX(R=H) gives the corresponding keto-acetate LXIX (R=Ac) under conditions identical to those used in the preparation of XCIII. Acid hydrolysis of XCIII at room temperature gave a mixture of starting material and a new keto-acetate, m.p. 140-142°. The latter showed maxima in the infrared at 1755 cm<sup>-1</sup> (OAc) and 1723 cm<sup>-1</sup> (ketone) and in the ultraviolet at 300 m $\mu$  (log  $\epsilon$  = 1.95). The optical rotatory dispersion spectrum showed a positive Cotton effect with extrema at 327 m $\mu$  (+1,800°) and 282 m $\mu$  (-10,900°). This data agrees with that expected for the O-acetate of alkaloid L.20 (LXXV, R=Ac).

Base catalyzed hydrolysis of the enol acetate XCIII, using aqueous sodium hydroxide at room temperature, gave alkaloid L.20 in 48% yield. The remainder of the reaction product appeared, from the infrared spectrum, to be a mixture of starting material, the unsaturated ketone LXXIV, and a keto-acetate. The scale of



the experiment prevented the identification of the keto-acetate.

The 6 $\alpha$ -acetoxy ketone LXXV (R=H), like the 6 $\alpha$ -hydroxy- and bromo-ketones, was found to be very susceptible to 1:4 elimination giving the  $\alpha,\beta$ -unsaturated ketone LXXIV on heating or on contact with wet solvents. In contrast to 6 $\alpha$ -bromolycopodine, however, this compound was reasonably stable in methanol, the amplitude of the Cotton effect being virtually unchanged after two days in that solvent.

Acid catalyzed hydrolysis of the keto-acetate LXXV (R=Ac), as expected on the basis of the above results, led to a mixture of the parent ketol L.20 and the unsaturated ketone LXXIV. Attempted epimerization of LXXV (R=H) to the 6 $\beta$ -acetoxy-ketone LXIX (R=Ac) on basic alumina gave a mixture whose infrared spectrum indicated a mixture of the unsaturated ketone LXXIV, a keto-acetate and a ketol. The unsaturated ketone is presumably formed by 1:4 elimination from the acetoxy compound LXXV (R=Ac), since it is known (see above) that L.20 gives largely the epimeric ketol LXIX (R=H) under similar conditions. From this knowledge it appears that the ketol obtained from LXXV (R=Ac) must also be LXIX (R=H). The keto-acetate in the mixture may be the 6 $\beta$ -acetate, since the peak at 1220 cm<sup>-1</sup> in the infrared spectrum of the mixture had a shoulder at 1240 cm<sup>-1</sup>, the latter being present in 6 $\beta$ -acetoxylycopodine LXIX (R=Ac) but not in LXXV (R=Ac). Again the scale of the experiment restricted isolation of pure products from the mixture.

The keto acetate LXXV (R=Ac) could be prepared directly from L.20 by acetylation with acetic anhydride-pyridine at -10°. Under these conditions the enol acetate XCIII was apparently not formed, although, not unexpectedly, infrared spectra indicated the formation





of the unsaturated ketone LXXIV in the reaction.

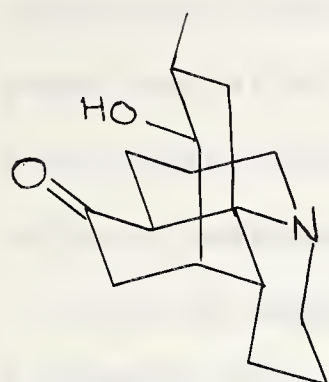
The acetolysis of the bromo-ketones XC and XCI was studied in an attempt to form the 6-acetoxy ketones by a more direct route. The 6 $\beta$ -bromo compound XCI.HBr on treatment, at reflux temperature, with acetic acid-acetic anhydride (100:1) containing sodium acetate gave a mixture which proved to be composed largely of the  $\alpha,\beta$ -unsaturated ketone LXXIV (62%) and the axial acetoxy ketone LXXV (R=Ac) (25%). The epimeric 6 $\alpha$ -bromolycopodine hydrobromide XC.HBr reacted to only a small extent under similar conditions. Under more severe conditions using as solvent, again at reflux temperature, acetic acid-acetic anhydride in a ratio of 3:1 the major product was the enol acetate XCIII, isolated in 41% yield. Small amounts of the unsaturated ketone LXXIV and the 6 $\alpha$ -acetoxy ketone LXXV (R=Ac) were isolated, but the total purified material obtained was less than 50% of the theoretical. The axial bromo compound presumably reacts more slowly than the epimer because of the necessity for prior epimerization, followed by normal backside attack. The equatorial acetoxy ketone LXIX (R=Ac) was not detected in either acetolysis, but the large amount of tarry residues prevented a complete study of the reaction products.

#### VI. THE OXIDATION OF THE BRIDGE RING IN LYCOPODINE.

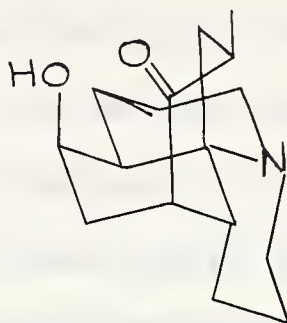
Among the alkaloids listed in the introduction to this dissertation are six with oxygen functions at C-5 and C-8, no other oxygen functions or unsaturations in the molecule and the same carbon-nitrogen skeleton as lycopodine. In addition, these alkaloids (fawcettiine XLIX, deacetylfawcettiine XLVIII, acetylfawcettiine (Base K) XCVI, annofoline LII, clavolonine XCVII and



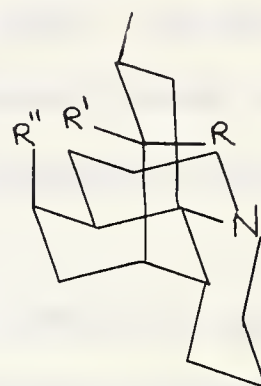
lofoline XCVIII) have stereochemistry at C-4, C-7, C-12 and C-13 identical to that of lycopodine (46, 66).



XCVII



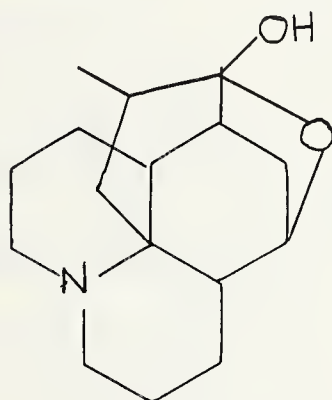
LII



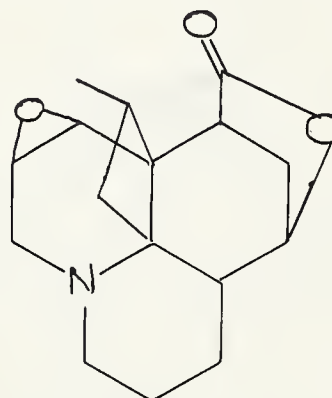
R R' R''

XLIX,	H	OAc	OH
XCVI,	H	OAc	OAc
XLVIII,	H	OH	OH
XCVIII,	OH	H	OAc

The possibility that the lycopodine carbon skeleton is the central intermediate in the biosynthesis of the Lycopodium alkaloids has been suggested (102) and the similarity between the hemiketal form of annofoline and annotinine has been pointed out (102).



Annofoline



Annotinine

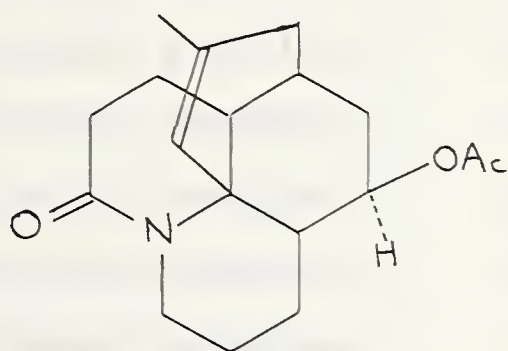
Possibly a compound of the lycopodine type oxygenated at C-5 is further oxidized in the plant at C-8 leading to such compounds as annofoline and perhaps even to compounds of the annotinine skeleton. For this reason we became interested in carrying out a similar transformation in the laboratory and it was for this



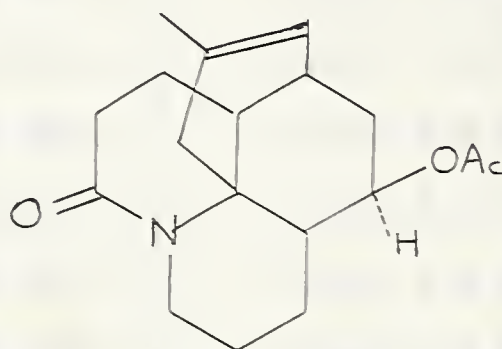


reason that we initially investigated the lead tetraacetate oxidation of the dihydrolactam XLI (see page 36) which as shown previously led to the 5,15-ether LIV in good yield. In this compound oxidation of the "bridging" ring has been achieved, but at C-15 rather than C-8, and we now set about to transform the ether into an intermediate oxidized at C-8.

It is known (68c) that ether linkages can often be cleaved by treatment with boron trifluoride-etherate in acetic anhydride. Di-secondary ethers usually give the corresponding diacetate (68c) but in our case, with a secondary, tertiary ether, we anticipated cleavage to the unsaturated secondary acetate. It was expected that proton loss might occur equally well from C-8 or C-14, leading to a mixture of the  $\Delta_{8,15}$  olefin XCIX and the  $\Delta_{14,15}$  olefin C. Either olefin could conceivably serve for the introduction of oxygen at C-8 (for example, Brown hydration or epoxidation of XCIX, allylic oxidation of C).



C



XCIX

Treatment of the ether LIV with excess boron trifluoride-etherate in acetic anhydride at room temperature did not, however, give the desired product. The major product, obtained after basification of the reaction mixture with ammonia and extraction with chloroform, was a basic compound, molecular weight 368 (from the



mass spectrum) which analyzed for  $C_{22}H_{28}O_3N_2$ . This compound, m.p. 167-167.5°, showed maxima in the infrared (nujol) at 1728 and 1240  $cm^{-1}$  attributed to O-acetyl), at 1639 and 1627  $cm^{-1}$  (occasionally a single peak at 1635  $cm^{-1}$ , attributed to the lactam carbonyl) and at 1590 and 1510  $cm^{-1}$ . The last two peaks suggested the presence of an aromatic ring. The ultraviolet spectrum showed peaks at 269  $m\mu$  ( $\log \epsilon = 3.63$ ) and 276  $m\mu$  ( $\log \epsilon = 3.60$ ) shifting to a single peak at 273  $m\mu$  ( $\log \epsilon = 3.91$ ) after acidification. This behavior is typical of pyridine and its alkyl substituted derivatives. The ultraviolet spectral data for several methyl and dimethyl pyridines are listed below (103).

Compound	pH > 7		pH = 1	
	$\lambda$	$\log \epsilon$	$\lambda$	$\log \epsilon$
Pyridine	251, 257	3.38, 3.42	256	3.73
2-methyl pyridine	255, 265, 270	3.4, 3.5, 3.4	262	3.72
3-methyl pyridine	255, 265, 280	3.4, 3.4, 3.3	262	3.74
4-methyl pyridine	255, 265	3.3, 3.2	261	3.72
2:3-dimethyl pyridine	265, 270	3.6, 3.5	267	3.9
2:4-dimethyl pyridine	259, 264	3.4, 3.3	259	3.8
2:5-dimethyl pyridine	268, 273	3.6, 3.4	268	3.8
2:6-dimethyl pyridine	266, 271	3.6, 3.5	269	3.9
3:4-dimethyl pyridine	259, 265	3.4, 3.3	258	3.7
3:5-dimethyl pyridine	268, 272	3.5, 3.4	268	3.8
Reaction Product	269, 276	3.63, 3.60	273	3.91

Comparison of this data with the ultraviolet spectra of our reaction product suggested that the  $C_{22}$  compound was a substituted pyridine and since the maxima occur at longer wavelength than any of the di-substituted compounds, probably at least trisubstituted. The fact





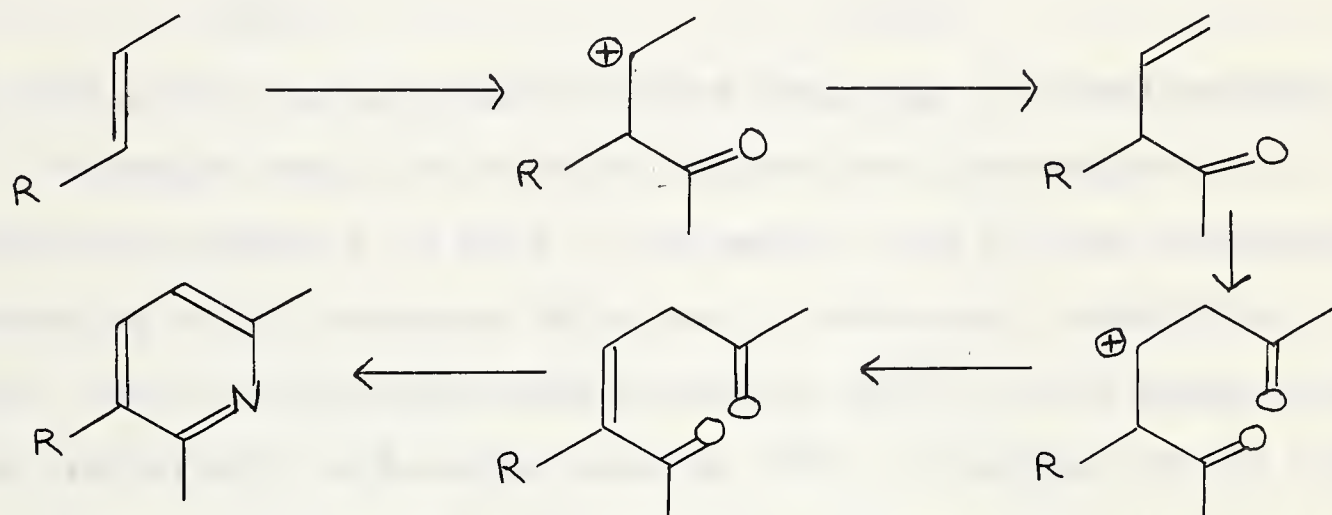
that it was actually tetrasubstituted was shown by the NMR spectrum which displayed a single aromatic proton at 3.18 $\tau$ . The NMR also showed signals at 7.55 $\tau$  (6H, two aromatic methyl groups) and 8.70 $\tau$  (3H,  $\text{OCOCH}_3$ ?)

Reduction of the amido pyridine with lithium aluminum hydride in ether yielded a crystalline basic product, m.p. 232-234°, which analyzed for  $\text{C}_{20}\text{H}_{28}\text{ON}_2$ . The mass spectrum showed a molecular weight of 312. The infrared spectrum (nujol) showed maxima at 3300  $\text{cm}^{-1}$  (hydroxyl) and 1592 and 1562  $\text{cm}^{-1}$  (aromatic compound) with no lactam or ester absorption as expected. The ultraviolet spectrum confirmed that the pyridine ring had been retained in the reduction, showing maxima at 268  $\text{m}\mu$  ( $\log \epsilon = 3.19$ ) and 276  $\text{m}\mu$  ( $\log \epsilon = 3.17$ ) shifting to a single peak at 275  $\text{m}\mu$  ( $\log \epsilon = 3.48$ ) on acidification. The NMR spectrum showed signals at 3.33 $\tau$  (1H, aromatic proton) and 7.61 $\tau$  (6H, two aromatic methyl groups). The signal at 8.70 $\tau$  was no longer present in the reduction product, suggesting that the assignment of this peak to the acetate methyl group is correct. Acetylation of the reduction product, using acetic anhydride-pyridine at 100°, gave a product whose NMR spectrum showed signals at 3.20 $\tau$  (1H, aromatic proton), 5.16 $\tau$  ( $\text{CHOAc}$ ), 7.58 and 7.60 $\tau$  (total of 6H, two aromatic methyl groups) and 8.78 $\tau$  (3H singlet). This last peak is presumably due to an O-acetyl group, confirming our original assignment. This methyl group absorbs at unusually high field and is presumably shielded to a great extent by the aromatic ring. The position of the signal attributed above to the aromatic proton indicates (98) that this proton is  $\beta$  to the pyridine nitrogen.

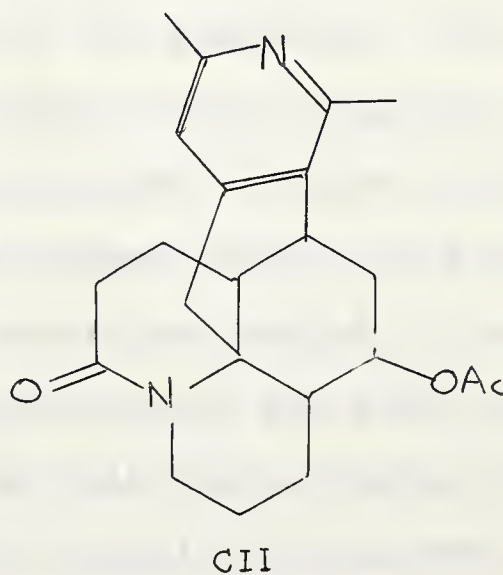
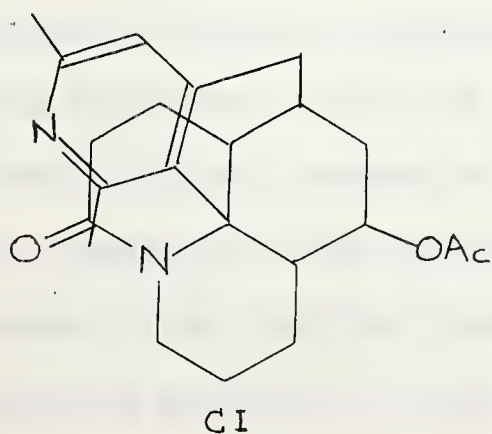
A possible explanation for the formation of the pyridine



derivative in the boron trifluoride etherate-acetic anhydride reaction was that initial cleavage of the 5:15 ether gave the unsaturated compound C and/or XCIX. A Friedel-Crafts type acylation of the olefin thus formed would lead, by the mechanism shown below, to a diketone which could then react with ammonia to give the pyridine.

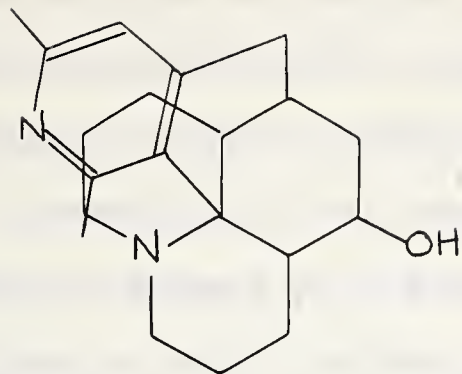


Although several examples of ring closure of saturated 1:5 diketones have been reported (99), few compounds analogous to the unsaturated diketone in the above scheme are readily available. The cyclization to the pyridine is, however, not unexpected (99). On the basis of this scheme the initial product isolated would be the pyridine CI (from the intermediate C) or the pyridine CII (from the intermediate XCIX) and the reduction product CIII or CIV.

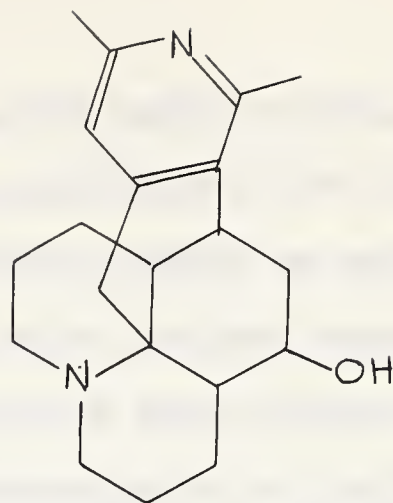








CIII



CIV

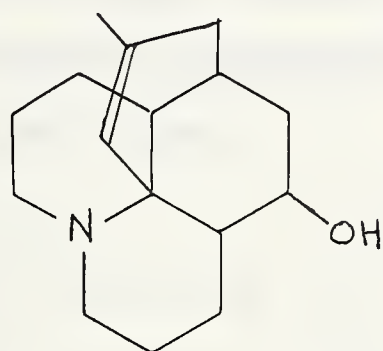
At this point the two possibilities could not be distinguished.

Attempts were then made to isolate the intermediate unsaturated acetate C or XCIX. The amido ether LIV was recovered unchanged after treatment with acetic acid-acetic anhydride at  $100^{\circ}$ , boron trifluoride etherate-acetic acid at room temperature and hydrobromic acid-acetic acid at  $100^{\circ}$ . Treatment of LIV with small amounts of boron trifluoride etherate-acetic anhydride in a large excess of ether, however, gave a non-crystalline neutral product which showed maxima in the infrared at  $1730$  and  $1227\text{ cm}^{-1}$  (acetyl) and  $1630$  and  $1635\text{ cm}^{-1}$  (lactam carbonyl). The NMR spectrum of the crude product showed signals at  $8.30\tau$  (3H, singlet,  $\text{C}=\text{C}-\text{CH}_3$ ),  $8.06\tau$  (3H singlet,  $\text{OCOCH}_3$ ),  $4.56\tau$  (doublet,  $J=6.5\text{ c.p.s.}$ ) and  $4.70\tau$  (singlet). The last two peaks which totalled one proton lie in the olefinic proton region of the spectrum. The doublet at  $4.56\tau$  accounted for the major part of this absorption. Consideration of the two possible unsaturated acetates C and XCIX suggests therefore that the major product in this case is XCIX since the olefinic proton at C-8 should be coupled to the C-7 proton, leading to the observed splitting of the  $4.56\tau$  peak. In the isomer C the olefinic proton at C-14 has no vicinal hydrogens and would be expected to give only a singlet in the NMR. On the

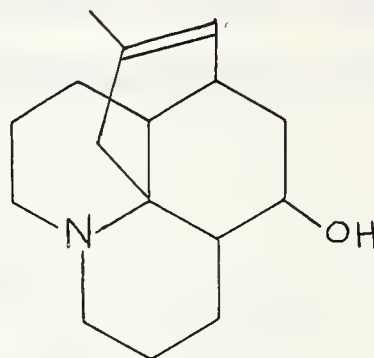


basis of this conclusion, therefore, the amido pyridine described above is probably CII, although the possibility that acylation of the minor olefin C leads to the pyridine cannot be excluded.

Reduction of the crude acetate which we now assumed to be largely composed of the  $\Delta_{8,15}$  olefin XCIX with lithium aluminum hydride in ether yielded, after chromatography of the crude product over alumina, a colorless oil in moderate yield. The infrared spectrum showed a maximum at  $3550\text{ cm}^{-1}$  and no carbonyl absorption indicating that reduction to the unsaturated alcohols CV and CVI was complete.



CV



CVI

Conversion to the perchlorate in acetone-ether gave a semi-crystalline salt which showed a maximum in the infrared at  $3490\text{ cm}^{-1}$  (nujol). This was reconverted to the free base, a mobile colorless oil, which showed signals in the NMR spectrum at  $8.33\tau$  (3H, doublet  $J < 0.1\text{ c.p.s.}$ ) attributed to  $\text{CH}=\text{CCH}_3$ , and at  $4.13\tau$  (1H, doublet  $J = 5.0\text{ c.p.s.}$ ). This low field peak is attributed to the olefinic proton in CVI for the reasons outlined in the discussion of the NMR spectrum of the acetate XCIX.

The unsaturated alcohol CVI whose mass spectrum indicated a molecular weight of 247 was not further investigated but it is clear that the preparation of this compound provides the key

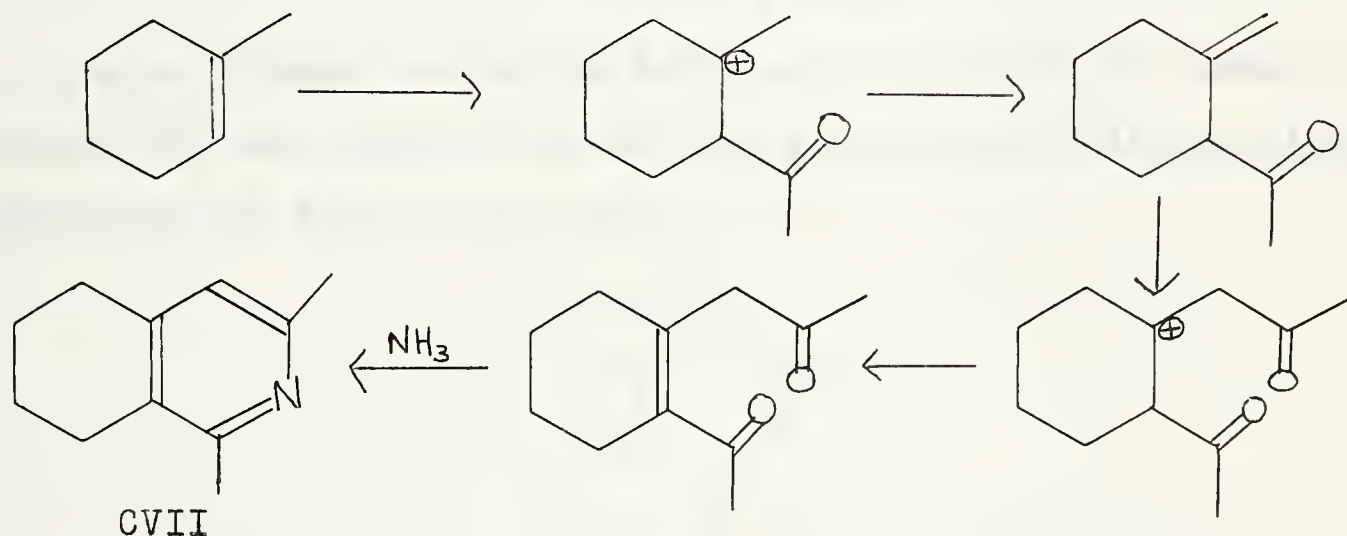




intermediate for a future partial synthesis of the C-5, C-8 dioxygenated alkaloids discussed earlier.

Treatment of the crude unsaturated acetate from the boron trifluoride-acetic anhydride-ether reaction above under conditions identical to those used in the conversion LIV  $\longrightarrow$  CII, gave the pyridine CII in good yield in agreement with the suggestion that the unsaturated acetate is the intermediate in the pyridine formation.

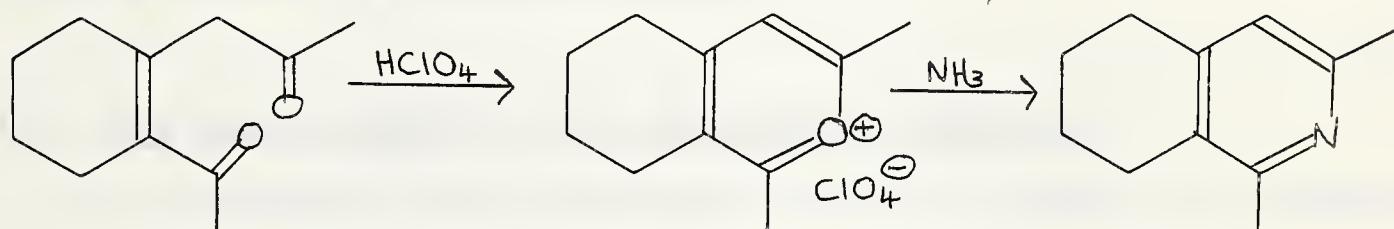
Our attention now turned to the reaction of boron trifluoride-acetic anhydride with 1-methyl cyclohexene. If the reaction above is general for methyl olefins the product in this case would be 5,6,7,8-tetrahydro,1:3dimethylisoquinoline CVII, formed by the route indicated below.



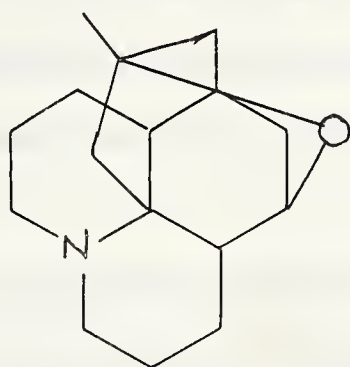
Treatment of 1-methylcyclohexene under conditions identical to those utilized for the conversion LIV  $\longrightarrow$  CII, gave a colorless oil, b.p. 84°/0.1 mm, molecular weight 161 (from mass spectrum) in 25% yield. The infrared spectrum showed maxima at 1590 and 1560 cm<sup>-1</sup> (film) while the ultraviolet spectrum showed peaks at 268 mμ (log ε=3.48) and 271 mμ (log ε=3.47) shifted to 273 mμ (log ε=3.78) on acidification. The NMR spectrum showed signals at



3.28 $\tau$  (one aromatic proton) and 7.57 $\tau$  (6H, singlet, two aromatic methyl groups). The picrate melted at 105-106° and the chloroplatinate at 221-222°. This method of preparation of tetrahydroisoquinolines proved not to be unique. Balaban and Nenitzescu (100) and Praill and Whitear (101) have prepared the same compound from 1-methyl cyclohexene using perchloric acid in place of boron trifluoride. In their case the melting point of the picrate was reported to be 124-125° and of the chloroplatinate 225°. These workers (100, 101 and references cited therein) have shown that the pyridines are formed by the action of ammonia on intermediate pyrylium salts, e.g.



In an attempt to find an alternative route to the unsaturated alcohol CVI the lactam ether LIV was reduced with lithium aluminum hydride to the basic ether CVIII.



CVIII

The ether CVIII, a colorless mobile oil, showed no absorption in the carbonyl or hydroxyl regions of the infrared spectrum. The mass spectrum showed that the molecular weight was 247 as expected. Treatment of the ether CVIII with boron trifluoride etherate-acetic anhydride appeared to give the corresponding pyridine derivative,





although only in moderate yield. The crude product showed maxima in the infrared (carbon tetrachloride) at 1728 and 1225  $\text{cm}^{-1}$  (O-acetate) as well as poorly defined peaks in the 1500-1600  $\text{cm}^{-1}$  region. The ultraviolet spectrum showed peaks at 268  $\text{m}\mu$  and 276  $\text{m}\mu$  shifting to a single peak at 273  $\text{m}\mu$  on acidification.

Further investigation of this reaction, in particular the actual introduction of oxygen at C-8 into the unsaturated compound XCIX or CVI, was not carried out at this time since our supplies of lycopodine had been exhausted. However, it appears that the preliminary objective, the oxidation of C-8 (in the form of the olefinic carbon) had been attained.

#### VII. THE MASS SPECTRA OF THE LYCOPODIUM ALKALOIDS.

It has already been mentioned that an alkaloid, m.p. 261-263°, which appeared from the infrared spectrum and analysis to be a  $\text{C}_{16}$  diol, was isolated in low yield from Lycopodium clavatum var. megastachyon. The amount of the alkaloid at hand prohibited extensive chemical degradation and the possibility of determining the structure, or at least partial structure, by other means was considered.

Mass spectrometry appeared particularly attractive (104), since only very small quantities of material are required. Several Lycopodium alkaloids were at hand and these too were studied in an attempt to understand the modes of fragmentation of compounds with the lycopodine skeleton. Only the alkaloids with the carbon-nitrogen skeleton of lycopodine will be discussed at this time. It was found that other alkaloids (e.g. annotinine,  $\alpha$  and  $\beta$ -obscurine, lycodine) gave quite different fragmentation patterns.



The mass spectra of the lycopodine-like alkaloids can be divided into two regions:

(a) below  $m/e$  of about 140. This lower region of the spectrum appears to be very similar in all cases, irrespective of the number and position of oxygen substituents or carbon-carbon unsaturations. The peaks fall into well defined groups, each with one or two major components. The latter are at  $m/e$  91, 79, 77, 67, 65, 55. The nature of these fragments will not be discussed at this time. The most important conclusion appears to be that this region can be used as a "fingerprint" region to identify a compound containing a lycopodine skeleton.

(b) above  $m/e$  of about 140. This region appears to be characteristic of the compound under consideration and it was felt that an understanding of the processes involved in the formation of these fragments might lead to a rapid insight into the structure of new or minor alkaloids with the lycopodine skeleton. This region will be discussed in detail for several of the alkaloids.

The nomenclature used to describe a peak should be explained at this point. A peak described as 190 (1.6) means that the fragment under consideration has a mass/charge ( $m/e$ ) ratio of 190 and that this peak constitutes 1.6 per cent of the total ions produced in the fragmentation. A peak described as M-57 means that this fragment is 57 mass units less than the molecular ion ( $M^+$ ).

The first compound studied was the unsubstituted deoxydihydrolycopodine ("lycopodane" XXXI). This compound showed the molecular ion at  $M^+ = 233$  (1.6) as expected. The major peaks in the higher region mentioned above were at 218 (0.25), 190 (1.6),

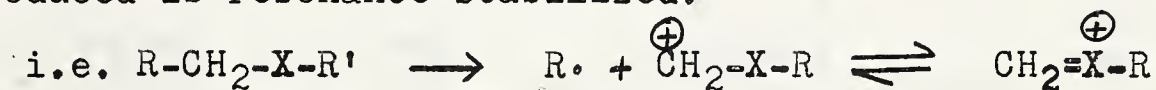




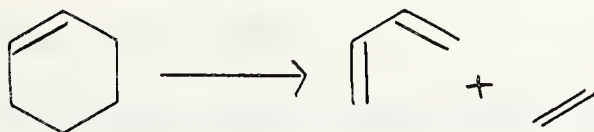
176 (42.7), 174 (2.3), 148 (1.6), 146 (0.8), 137 (1.3) and 136 (1.1).

It is known (105) that three "favored fragmentations" are:  
(i) cleavage at a tertiary carbon, since the resulting tertiary carbonium ion is relatively stable.

(ii) cleavage of the  $\alpha, \beta$  bond in hetero-compounds, since the ion produced is resonance stabilized.



(iii) elimination of ethylene from a cyclic olefin.

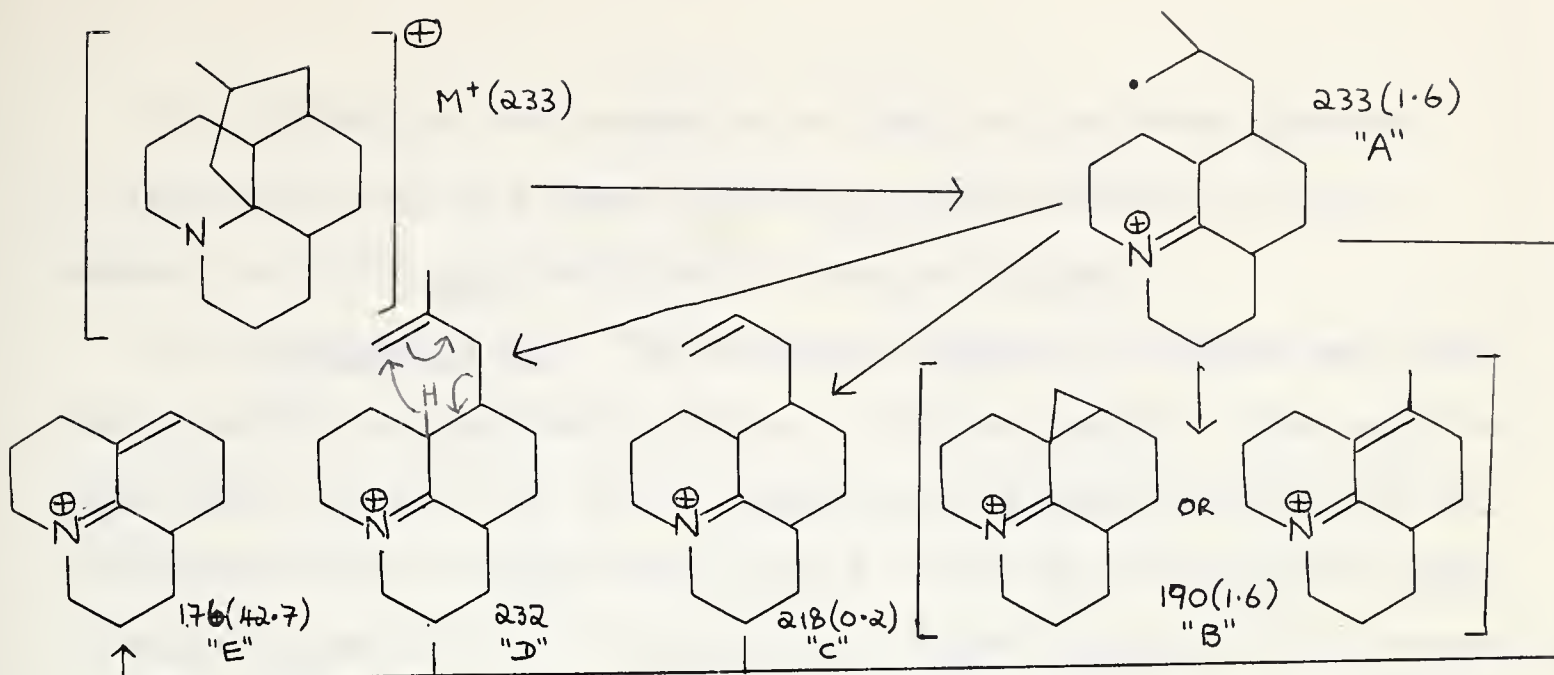


The elimination of water from alcohols and acetic acid from acetates is also well known (104). These and other well authenticated rearrangements (104) will be dealt with without further discussion below.

Returning now to the mass spectrum of "lycopodane", the peak at  $m/e$  218 corresponds to  $M-15$  and is presumably due to a fragment formed by loss of the C-methyl group of lycopodane. By far the largest peak in the spectrum is at  $m/e$  176 (42.7% of the total ions) and corresponds to  $M-57$ .

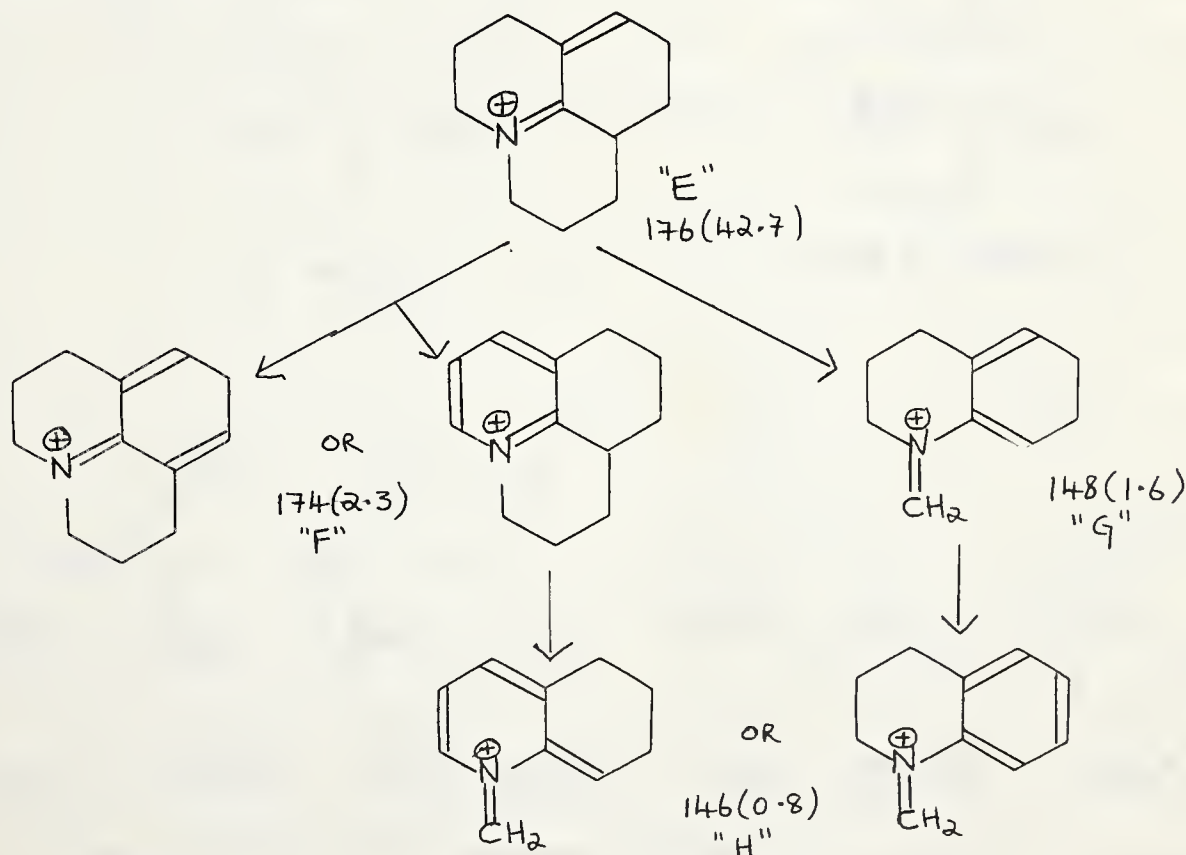
A possible sequence which would give rise to ions with the correct mass is outlined in the following scheme.





Fragmentations of type "A"  $\longrightarrow$  "E" are known (106), as are "D"  $\longrightarrow$  "E" types (105, 106).

Fragment "E" could then conceivably lose either  $H_2$  to give fragment "F" (found  $m/e$  174 (2.3)) or ethylene to give ion "G" (found  $m/e$  148 (1.6)). Ions "F" and "G" could then lose ethylene or  $H_2$  respectively to give the ion "H" of mass 146 (found  $m/e$  146 (0.8)). This possible sequence is illustrated with the following structures.

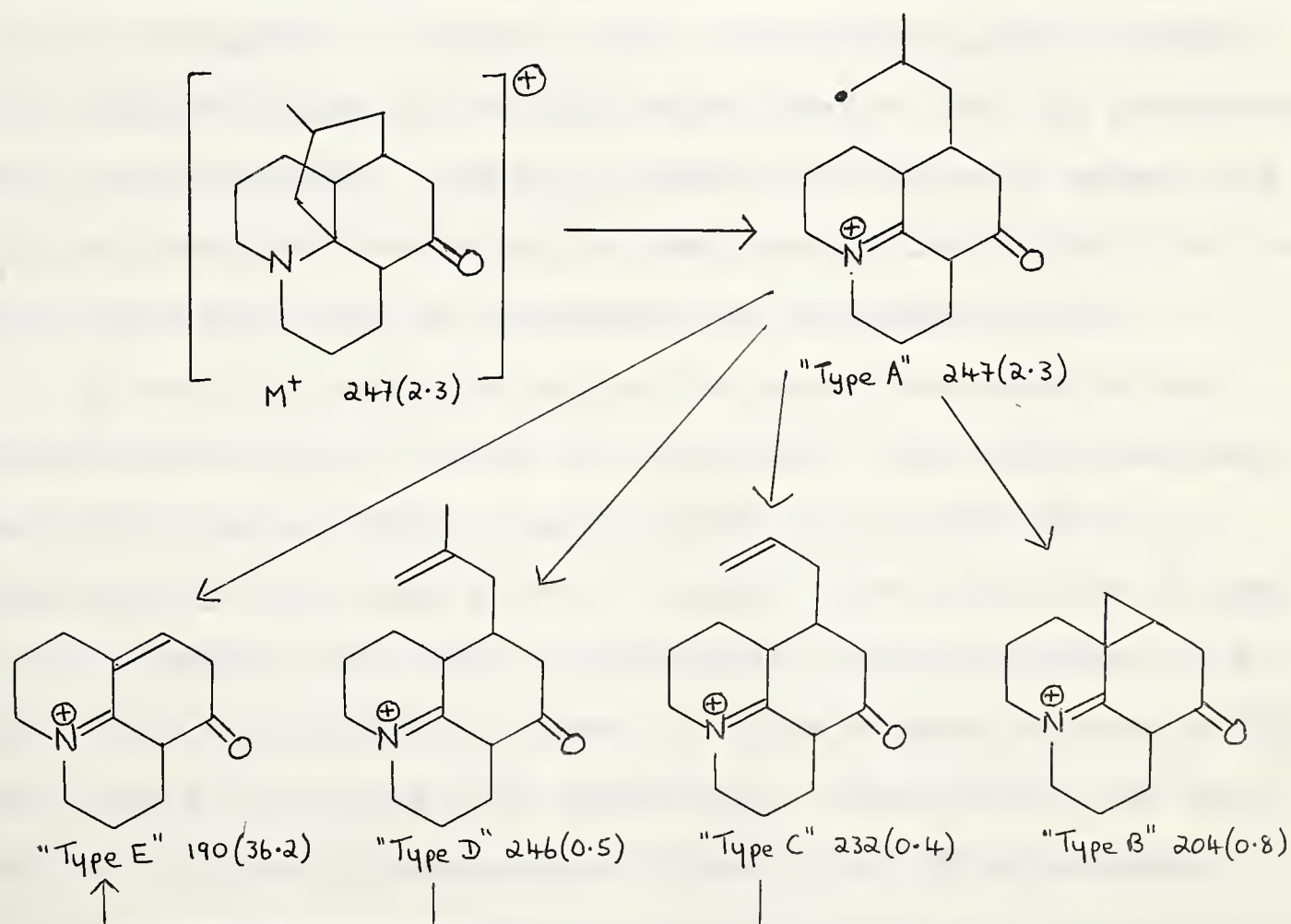




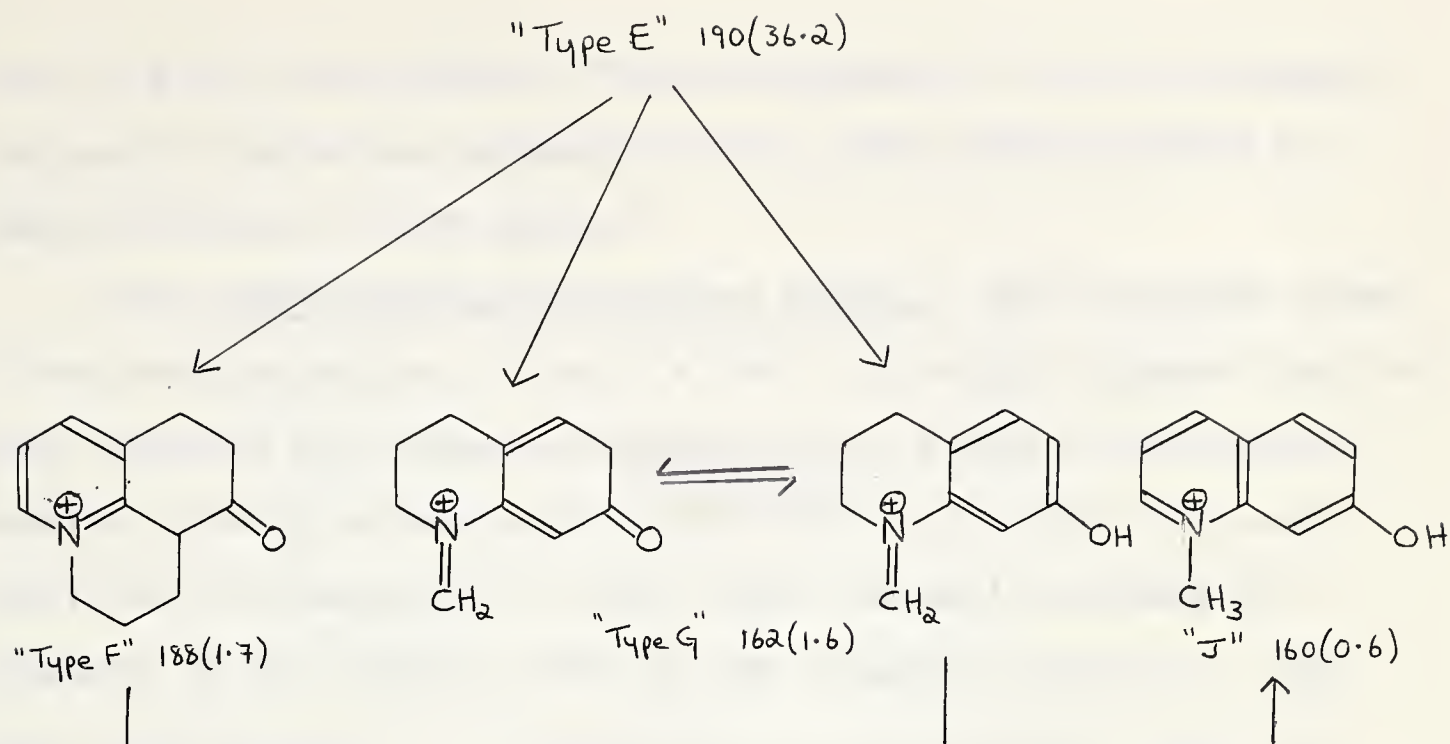


Our attention now turned to a study of the mass spectra of compounds with the same carbon-nitrogen skeleton as lycopodane, but with one additional functional group.

(i) Lycopodine XX. The spectrum appeared to agree well with the tentative fragmentation pattern outlined above. The most intense peak, at  $m/e$  190 (36.2), again corresponds to M-57 and, on the basis of the scheme above, would be an ion of "type E", with an oxygen atom at C-5. With similar oxygen insertion the lycopodine peak at  $m/e$  246 (0.5) could correspond to an ion of "type D", that at 232 (0.4) to "type C", that at 204 (0.8) to "type B", that at 188 (1.7) to "type F", that at 162 (1.6) to "type G" and that at 160 (0.6) to "type J". The possible scheme for lycopodine can thus be represented by the following structures.







(ii) Dihydrolycopodine XXIX. It has already been stated that hydroxy compounds readily lose the elements of water. If the proposed scheme, with the oxygenated ring retained throughout the high molecular weight fragments, is correct one would predict two types of fragments. Firstly, with the hydroxyl group retained, the fragments would be two mass units greater than the corresponding lycopodine peak. Secondly, after elimination of water, the fragment would be sixteen units less than in lycopodine (i.e. two mass units less than the corresponding lycopodane peak).

In the high molecular weight fragments the spectrum was indeed very similar to that of lycopodine. The intense maximum due to the ion of "type E" was located at  $m/e$  192 (26.8) as predicted by the scheme above. The fact that this "type E" peak is less intense than that in lycopodine can be accounted for by the facile elimination of water. A "type E" peak located at 174 (3.7) would accommodate this prediction. Peaks at  $m/e$  190 (4.4) and 146 (1.9) could be assigned "type F" and "H" structures.

The spectrum showed peaks, with intensities of approximately





0.3, at M-17, M-18, M-19. This was typical of all the hydroxy compounds studied and appears to be a good general method of identification of that group.

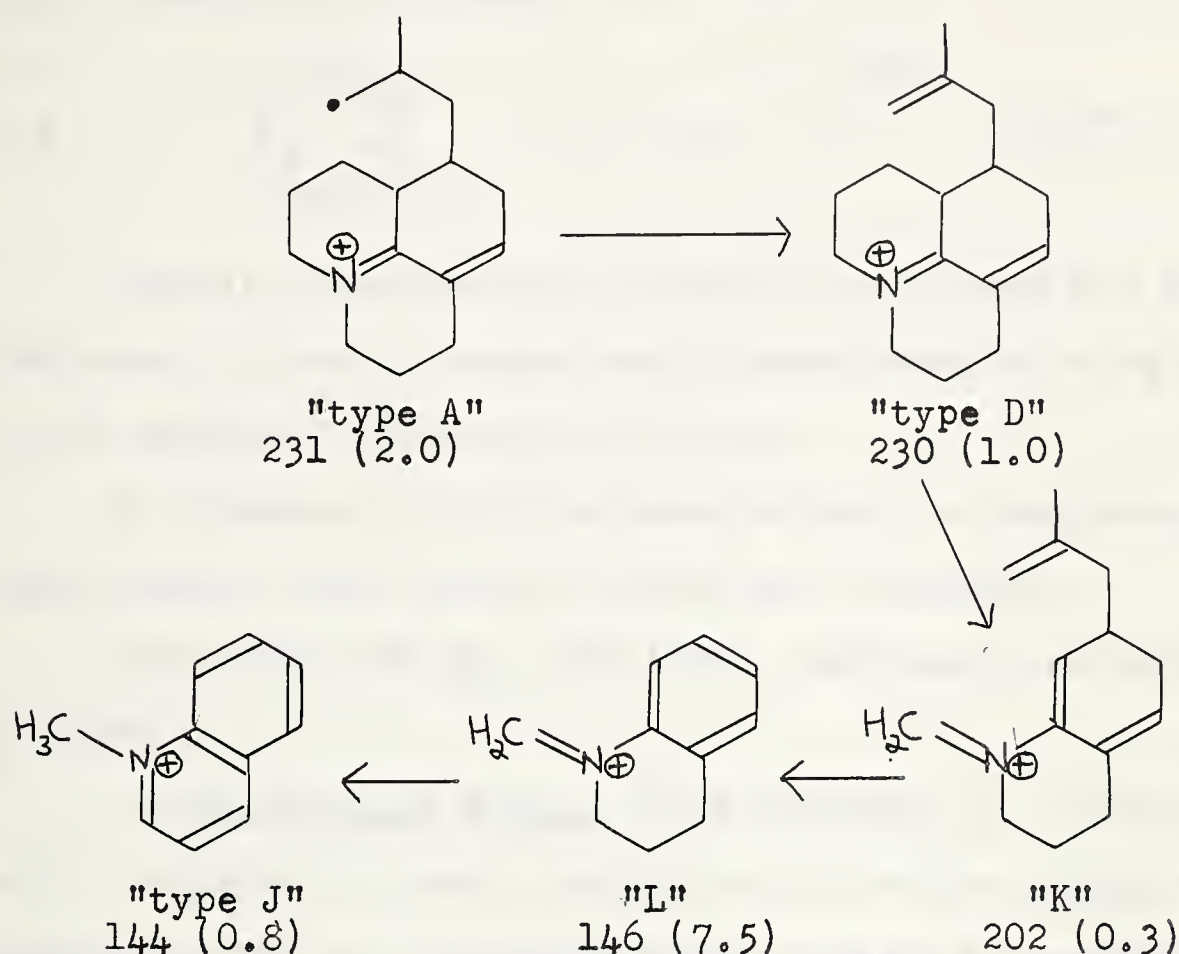
(iii) O-Acetyldihydrolycopodine XXXIII. This compound shows a very weak molecular ion at  $m/e$  291 (0.2) which appears from the data obtained from other acetates in this series to be typical. However, fairly strong peaks at  $m/e$  232 (0.5), 231 (2.0) and 230 (1.0) corresponding to M-59, M-60 and M-61 indicate the presence of the acetate group in the original compound. This fact, which appears to be general, is particularly useful in those cases where the  $M^+$  peak is very weak or even absent, in that it can be utilized not only to identify the functional group but also to help establish the molecular weight.

Many of the other fragment masses can be explained by the scheme above. The most intense peak appears at  $m/e$  174 (23.9) and could be ion "F" formed by loss of the bridge ring and acetic acid. If the bridge ring is lost first it gives an ion of mass 234, "type E", (found  $m/e$  234 (0.8)), if the acetic acid is first eliminated the ion remaining, of "type A", has a mass of 231 (found  $m/e$  231 (2.0)) which could lose  $H\cdot$  to give a "type D" ion (found  $m/e$  230 (1.0)). The peak at  $m/e$  188 (1.6) could again be attributed to an ion of "type B" (with  $\Delta_{4,5}$  unsaturation) and that at 146 (7.5) to ion "H". The latter could lose  $H_2$  to give the aromatic "type J" ion (found  $m/e$  144 (0.8)).

An alternative route from the "type D" ion involves loss of ethylene to give ion "K",  $m/e$  202 (found 202 (0.3)). The peaks at 146 and 144 could then also be explained by loss of the side chain and, subsequently,  $H_2$  from "K", giving ions "L" and "type J".



This alternative would also be possible in the lycopodane fragmentation (found 204 (0.7)) and lycopodine (found 218 (0.2)).



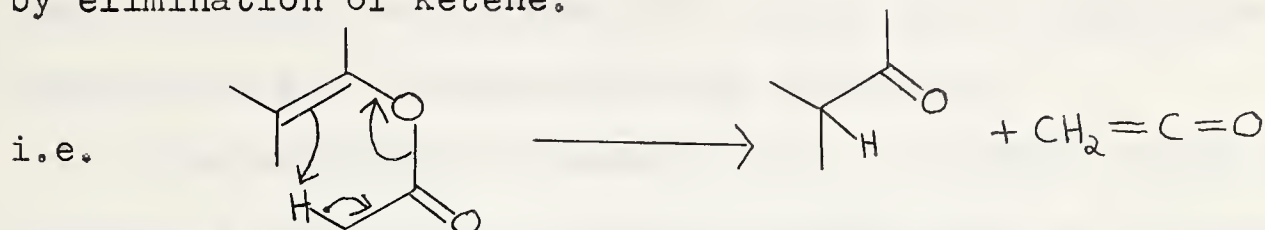
(iv) Anhydrodihydrolycopodine XXXV. If the scheme outlined above for O-acetyldihydrolycopodine is correct (with one alternative involving loss of acetic acid to give anhydrodihydrolycopodine) then one would expect a close similarity in the spectra of the two compounds. This was indeed the case. The two spectra were virtually the same, although anhydrodihydrolycopodine had more intense peaks at m/e 202 (2.4), 146 (11.6) and 144 (1.0). This is readily explained since the competitive formation of the "type D" ion is no longer required. Instead this ion is formed directly by opening of the bridge ring.

(v) Lycopodine enol-acetate XCV. The two most intense peaks were located at m/e 232 (12.1) (corresponding to loss of the





bridge ring) and at 190 (27.9). This ion could be accommodated with a "type E" structure being formed from the ion of mass 232 by elimination of ketene.



Initial formation of a "type B" ion (found  $m/e$  246 (1.3)) followed by loss of ketene would leave another "type B" ion (with a C-5 carbonyl) found  $m/e$  204 (2.3).

In agreement with this postulation the remainder of the spectrum was very similar to that of lycopodine.

Compounds with two additional functional groups were now studied:

(i) Clavolonine XCVII. This compound is a hydroxy lycopodine with the hydroxyl group located at C-8 on the bridge ring. In agreement with our tentative scheme the mass spectrum of clavolonine was found to be virtually identical to that of lycopodine with the exception of the molecular ion (263 (0.7)) and a peak at 220 (0.5), the latter attributed to a "type B" ion with the hydroxyl group on the cyclopropane ring (or its equivalent).

(ii) Dihydroclavolonine. The mass spectrum of this compound was virtually identical to that of dihydrolycopodine with the exception of the molecular ion peak at  $m/e$  265 (0.2) and peaks at M-17 (0.5), M-18 (1.1) and M-19 (0.9) corresponding to loss of water. The scheme suggested above predicts initial loss of the bridge ring which would give the ion of "type E" identical to that from dihydrolycopodine in agreement with the observed spectrum.



At this point our attention turned to the mass spectra of 5-deuterodihydrolycopodine and 5-deuterodihydroclavolonine. These compounds were prepared by reduction of lycopodine and clavolonine with lithium aluminum deuteride.

5-Deuterodihydrolycopodine gave a molecular ion of mass 250 (found  $m/e$  250 (0.9)). The most intense peak in the spectrum was at  $m/e$  193 (19.9) corresponding to a "type E" ion. Loss of water from this ion would explain the observed peak at  $m/e$  175 (5.4). The fact that both these peaks are one mass unit greater than the corresponding peaks in dihydrolycopodine is in good agreement with the general scheme. A peak at  $m/e$  147 (1.8) in the deuterated compound is also one mass unit higher than the corresponding peak in dihydrolycopodine and could be explained by a "type H" ion. Below  $m/e$  140 the two spectra were identical. However, the possibility that an alternative route is also used in the higher region cannot be excluded. The deuterated material appeared to be fairly pure on the basis of the relatively small peaks at  $m/e$  192 (3.5) indicating not more than a trace of the undeuterated material and at  $m/e$  190 (5.0) indicating that reduction was complete. (This was also shown from the lack of carbonyl absorption in the infrared and the melting point, 169°, which showed no depression on admixture with authentic dihydrolycopodine). However, the mass spectrum of the 5-deuterodihydrolycopodine showed peaks at  $m/e$  174 (4.5) and 146 (2.2), one mass unit below the peaks described above, suggesting either different fragmentation patterns or hydrogen-deuterium exchange prior to the formation of the ions under consideration.

5-Deuterodihydroclavolonine appeared to behave in a similar



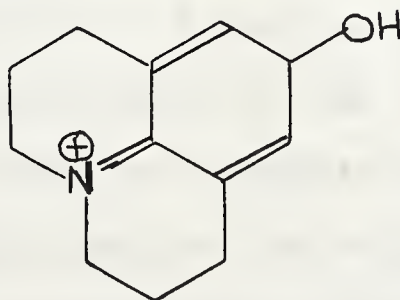


fashion. The most intense peak was located at  $m/e$  193 (17.7) corresponding to loss of the bridge ring and formation of a "type E" ion. Below this point the spectrum was almost identical to that of 5-deuterodihydrolycopodine.

(iii) Flabelliformine (4 $\alpha$ -hydroxylycopodine). A peak at  $m/e$  206 (1.7) agrees with the prediction that the bridge ring can readily be eliminated to form a "type E" ion. In this compound the most intense fragment was located at  $m/e$  188 (10.8) suggesting that the tertiary alcohol readily eliminates water to give an  $\alpha,\beta$ -unsaturated ketone of "type E". That this elimination is facile is shown by peaks at M-17 (0.9), M-18 (0.8) and M-19 (0.4). Loss of the bridge ring and the three carbon chain C-1, C-2, C-3 with retention of the hydroxyl group would lead to a fragment of mass 164 (found  $m/e$  164 (5.3)).

(iv) 6 $\beta$ -Hydroxylycopodine. A scheme similar to that suggested for lycopodine with retention of the secondary hydroxyl group appears to explain the major fragments in this case.

(v) Lycoclavine LXVII (R=Ac, R'=H). This compound showed a very small molecular ion but peaks at M-59 (0.4), M-60 (2.3) and M-61 (3.3) indicate ready loss of acetic acid. Loss of the bridge ring would then give ion "M" (found  $m/e$  190 (11.1)).



"M" 190 (11.1)



An alternate route, loss of the bridge ring and water followed by elimination of ketene from the resulting enol acetate, would give an m/e 190 peak identical to the "type E" ion formed from lycopodine.

Elimination of water from ion "M" would give a fragment of mass 172 (found m/e 172(3.6)) while loss of ethylene from ion "M" would give a "type G" ion (found m/e 162 (3.4)). These two ions could lose ethylene or water respectively to give the observed fragment at m/e 144 (0.7), a "type J" ion.

(vi)  $\alpha$ -Lofoline XCVIII. The mass spectrum of this alkaloid can be very well explained on the basis of our tentative scheme. The molecular ion m/e 307 as expected for an acetate gave a very small peak. Peaks at M-58, M-59 and M-60 correspond to loss of acetic acid, while a peak at m/e 234 (1.4) corresponds to loss of the bridge ring. These two fragments, by loss of the bridge or acetic acid respectively, would give a fragment of "type F" identical to that obtained from O-acetyldihydroxylycopodine (found m/e 174 (24.6)). In agreement with the theory the spectra of the two compounds were virtually identical below this point.

#### C-12 SUBSTITUTED COMPOUNDS

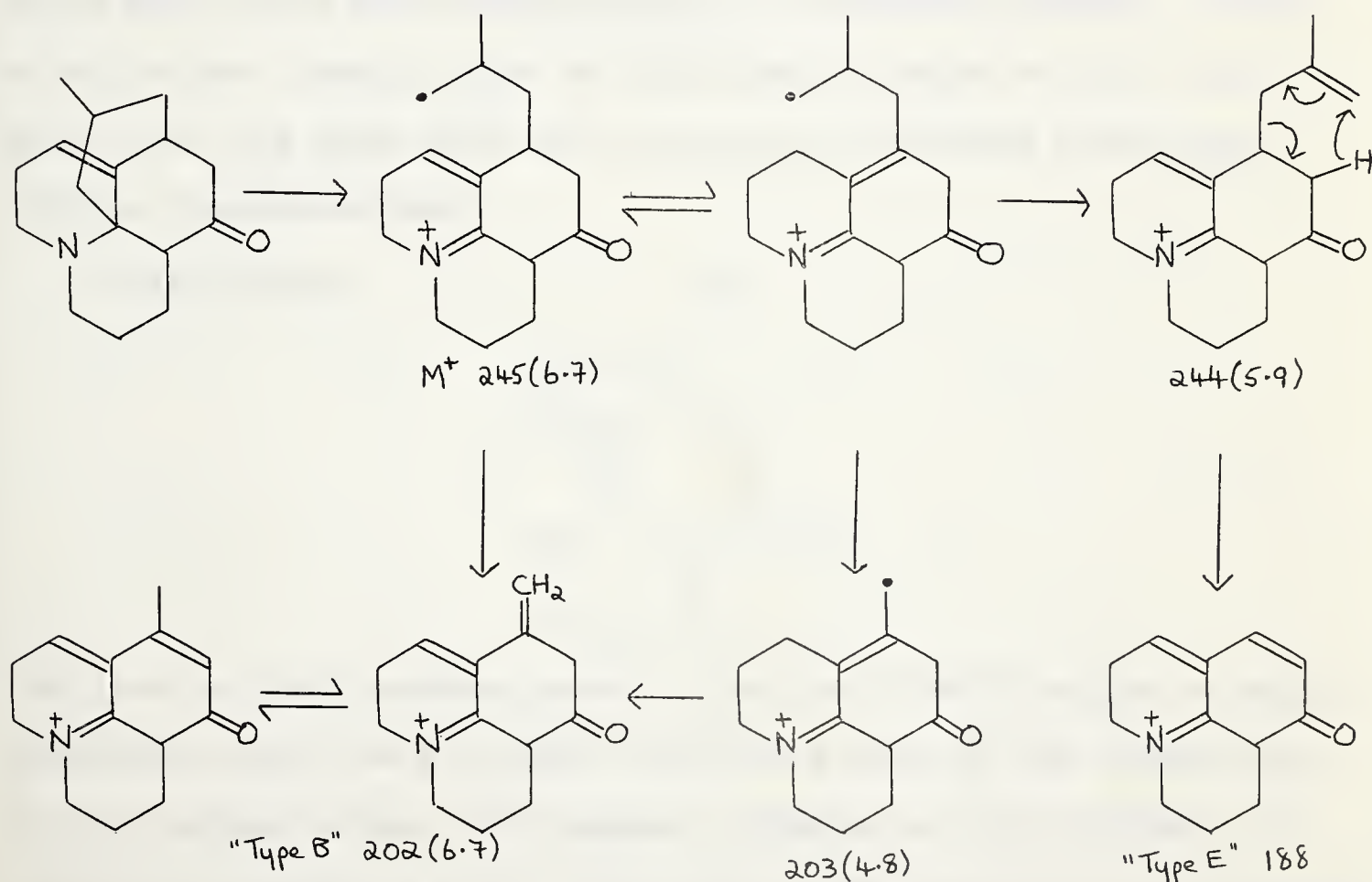
It has been demonstrated above that alkaloids with a lycopodine skeleton and a C-12 hydrogen atom may very well readily lose the bridge ring to give an intense fragmentation peak. The mass lost from the parent ion on formation of this fragment may indicate the degree of substitution of the bridge ring. For example, clavolonine and related compounds gave strong peaks at M-73 indicating a hydroxyl group on the bridge.

On the basis of the scheme above a different pattern was

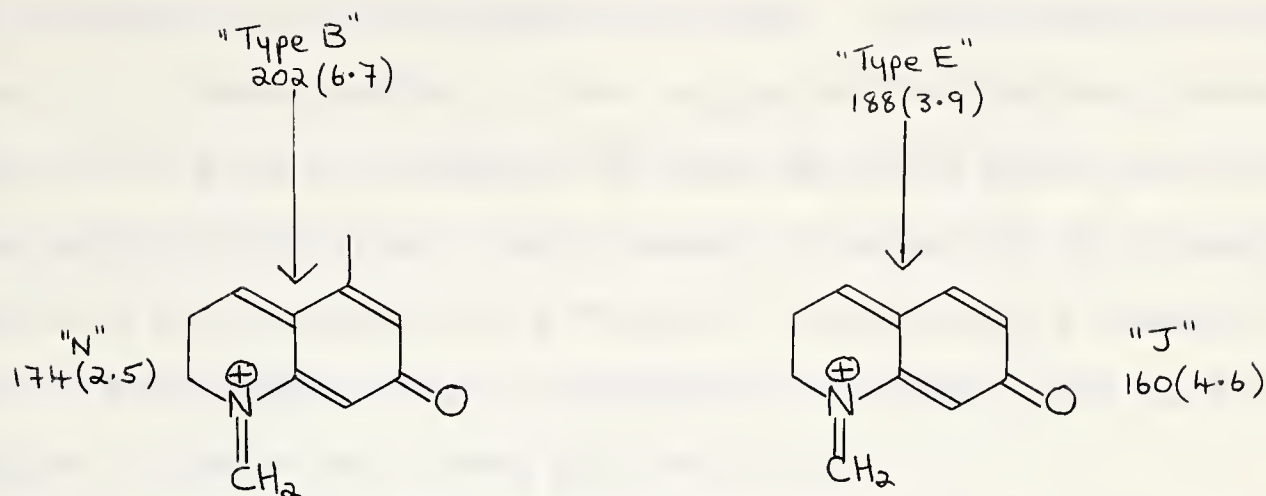




predicted for those alkaloids with substituents at C-12 since the hydrogen necessary for the extremely facile elimination of the bridge ring (a possible mechanism is indicated in ion "D" above) is no longer available. In fact it was found that in anhydrolycodoline (11,12- dehydrolycopodine), the strongest peak in the spectrum was that due to the molecular ion ( $m/e$  245 (6.7)). Initial cleavage of the 13,14 bond leads directly to a conjugated "Type A" ion as shown below. The largest fragment peak is now found at  $m/e$  202 and this is accompanied by a strong peak at  $m/e$  203 (the odd molecular weight indicating a radical ion). Since this pair of peaks occurs again in the spectrum of the "unknown diol" a possible route for their formation is outlined in the scheme below, which gives the major peaks found in the spectrum.



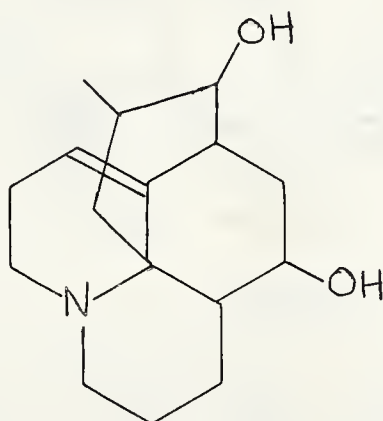




Although other schemes could account for the observed fragment masses the pattern above is particularly attractive in that the ion "J" has already been postulated in the fragmentation of lycopodine. The mass spectra of lycopodine and dehydrolycodoline are indeed almost identical below  $m/e$  160.

Lycodoline (12-hydroxyllycopodine) although very similar in the lower region of the spectrum shows many major peaks shifted by 18 mass units from similar peaks in dehydrolycodoline. Loss of water can clearly occur as indicated by peaks at M-17 (4.0), M-18 (0.4) and M-19 (0.6) but can also be retained during the initial fragmentations.

### Acrifolinol



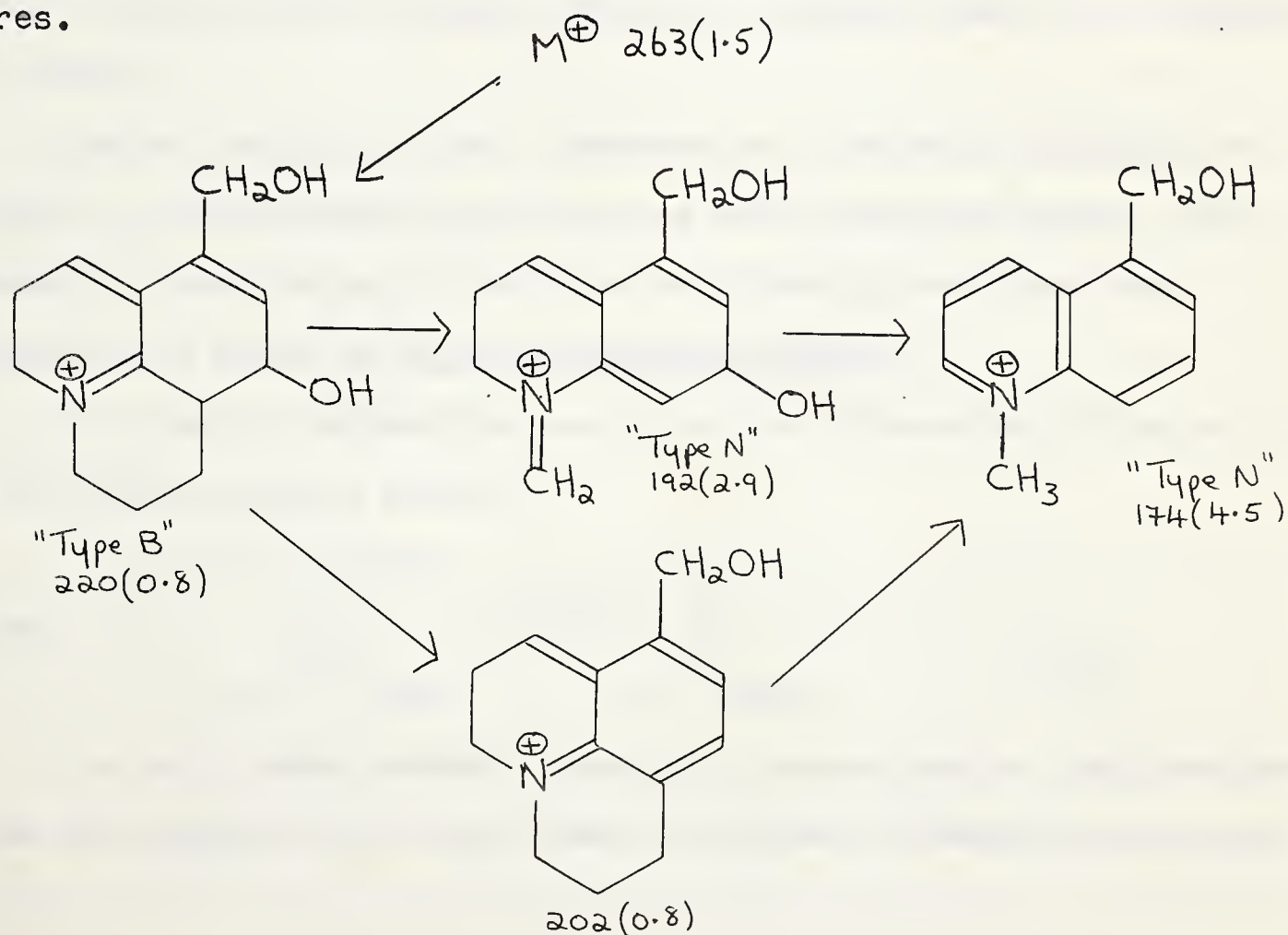
The lack of very intense peaks in the  $m/e$  170-200 region is again consistent with the view that the facile loss of the bridge ring is not favored unless the compound contains a C-12 hydrogen. In acrifolinol peaks at M-17 (1.6), M-18 (1.9) and M-19 (1.2) suggest





the elimination of the elements of water. In this event fragmentation by a route similar to that suggested for dehydrolycodoline should give rise to fragments of mass 16 units lower than those from dehydrolycodoline. The fragment of mass 172 (2.3) could therefore be attributed to a "type E" ion with  $\Delta_{4,5}$  unsaturation. Loss of the bridge without elimination of water would give a fragment of mass 190 (found m/e 190 (2.2)).

An alternate route could give rise to a "type B" ion with a hydroxymethyl group retained which could lose ethylene to give a "type N" ion, mass 192, which could subsequently lose water to give another "type N" ion of mass 174, thus accounting for the most intense peak in the spectrum. Loss of water prior to the elimination of ethylene would account for the observed fragment of mass 202. This scheme is represented by the following structures.





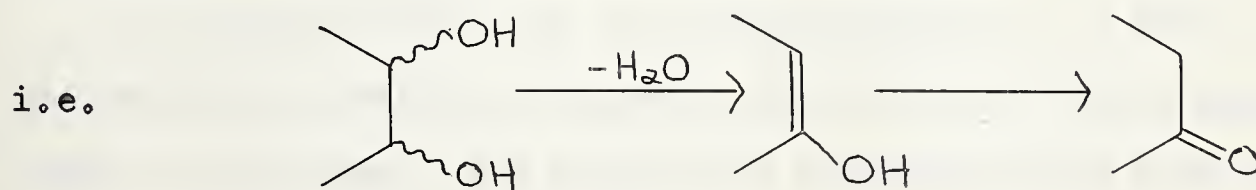
The new diol from *Lycopodium clavatum* var. *megastachyon*.

This compound exhibits a maximum in the infrared (nujol) at  $3380\text{ cm}^{-1}$  and a broad band at  $2500\text{--}3200\text{ cm}^{-1}$  indicating the presence of hydroxyl group(s). The lack of carbonyl absorption in the infrared, together with analytical data, which suggested the molecular formula  $\text{C}_{16}\text{H}_{25}\text{--}27\text{O}_2\text{N}$  indicated that the alkaloid was either a diol or a hydroxy ether. The small quantity of material, coupled with the insoluble nature of the compound, made it impossible to obtain a useful NMR spectrum.

The mass spectrum showed a molecular ion at  $m/e$  263, proving the molecular formula  $\text{C}_{16}\text{H}_{25}\text{C}_2\text{N}$ . This shows that if the compound is a diol and, like most lycopodium alkaloids, tetracyclic, it must contain one additional double bond. The mass spectrum showed a peak at  $m/e$  263 (2.2) and peaks at  $M-17$  (1.1),  $M-18$  (0.2) and  $M-19$  (0.3) indicating facile elimination of the elements of water.

Below  $m/e$  204 the mass spectrum was virtually identical to that of anhydrolycodoline which has been discussed above. The immediate conclusion is that the new alkaloid can lose the elements of water to give anhydrolycodoline.

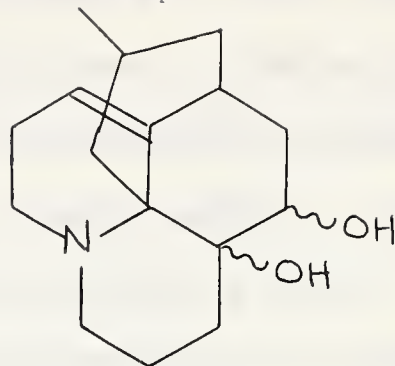
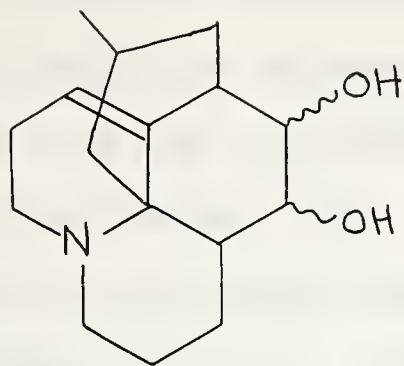
A possible explanation would be the elimination of water from a 1:2 diol giving a ketone.



In this event, without regard to stereochemical implications the new alkaloid could have one of the two following structures:







The mass spectrum of desacetylyllycoclavine LXXVIII was studied in an attempt to add credence to these conclusions. If the elimination of water from this type of system readily gives the ketone, the mass spectrum of desacetylyllycoclavine should be identical in all but the highest peaks to that of lycopodine. This prediction was vindicated since the mass spectra of desacetylyllycoclavine and lycopodine are in fact identical below  $m/e$  150. Above this point the differences can readily be explained by the fragmentation pattern proposed above. The most intense fragment in the spectrum of desacetylyllycoclavine is located at  $m/e$  208 (13.8), which could be accounted for by a "type E" ion, formed by loss of the bridge ring with retention of both hydroxyl groups. Water can readily be eliminated as indicated by peaks at  $M-17$  (0.1),  $M-18$  (0.5) and  $M-19$  (0.9). Elimination of water from the fragment of mass 208 would account for the observed peak at  $m/e$  190 (4.4).

The possibility that the new alkaloid is, in fact, 11-dehydro-desacetylyllycoclavine warranted a synthesis of this compound for direct comparison. The best route appeared to be from anhydrolycodoline (dehydrolycopodine) using the stages described above for the preparation of desacetylyllycoclavine from lycopodine, but lack of sufficient quantities of anhydrolycodoline or lykodoline



have prohibited any attempts at this synthesis to this time.

Although the evidence above is sufficient to tentatively suggest that the new alkaloid is a 5:6 dihydroxyllycopodine derivative several other possibilities clearly exist. The mass spectrum of the  $5\alpha,6\beta$  diol LXXIX was studied for purposes of comparison. The mass spectrum of the diequatorial diol LXXIX was very similar to that of the diaxial diol desacetyllycoclavine. The relative intensities of several peaks are different in the two spectra, but it is clear that the fragmentation pattern proposed above can explain the spectra of both compounds. The fact that the only known naturally occurring 5:6 dihydroxylated derivatives of lycopodine are the diaxial compounds in the lycoclavine series appears sufficient to justify a synthesis of the corresponding  $\Delta^{11}$  compound since the diol of unknown structure does occur in the same plant as lycoclavine.

In conclusion, mass spectrometry appears to be a good method of gaining insight into the structures of some Lycopodium alkaloids. The lycopodine skeleton can apparently be distinguished from other skeleta and some knowledge of the degree of substitution and even the position of substituents can be gained from comparison of the mass spectra with those of the compounds discussed in this section. It should also be mentioned that the determination of the exact molecular weight (most of the compounds in the series give recognizable parent peaks) is, of course, also extremely useful.





## EXPERIMENTAL

Ultraviolet absorption spectra were determined in 95% ethanol unless otherwise stated.

Optical rotatory dispersion spectra were measured on a Rudolph Automatic Recording Spectropolarimeter.

Nuclear magnetic resonance spectra were measured on  $\overline{\text{ca.}}$  10% w/v solutions in chloroform or deuterio-chloroform using a Varian Associates Model A-60 spectrometer with tetramethylsilane as an internal standard.

Melting points were determined on a hot-stage and are uncorrected.

Alumina, unless otherwise specified, means basic alumina of activity III-IV (Brockmann scale).

Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62-70°.

Microanalyses are by Pascher Mikroanalytisches Laboratorium, Bonn, West Germany, and C. Daessle, Montreal, Quebec.



THE N-FORMYL KETO ACID II

Solid potassium permanganate (2.15 g.) was added over a period of thirty minutes to a stirred, ice-cold solution of lycopodine (0.998 g.) and oxalic acid (0.513 g.) in distilled water (50 ml.). The mixture was stirred at room temperature for a further three hours, cooled to 0°, and gaseous sulphur dioxide passed through the suspension, resulting in a clear pale yellow solution.

The acidic solution was extracted six times with chloroform to remove acidic and neutral products. These were separated by shaking the combined organic extracts twice with aqueous ammonia, acidifying the latter with dilute hydrochloric acid and extracting again with chloroform to remove acidic products.

Neutral material remained in the original chloroform extract.

Basic products were obtained by basification of the original aqueous solution with aqueous ammonia, followed by continuous ether extraction for two days. The basic material obtained was found to be unreacted lycopodine (0.304 g.).

The neutral material (0.163 g.) was not investigated in detail. Infrared spectra which showed maxima at 1645, 1670, 1715, 3450 and 3620  $\text{cm}^{-1}$  (in chloroform) suggested the presence of lactam(s) and/or hydroxylated lactams.

The solid acidic product was crystallized from ether to give the pure acid II (0.309 g.) as short colorless needles. Two more crystallizations, followed by sublimation, furnished the analytical sample, m.p. 244-245°. Infrared spectra showed maxima at 1740, 1715 and 1638  $\text{cm}^{-1}$  (nujol mull) and at 1712, 1650 and 1615  $\text{cm}^{-1}$





(chloroform) together with a broad acid band at 2500-3500  $\text{cm}^{-1}$  in both cases.

Found C-65.38, 64.82%: H-7.65, 7.77%: O-21.83%: N-5.10%

$\text{C}_{16}\text{H}_{23}\text{O}_4\text{N}$  requires C-65.53%: H-7.85%: O-21.84%: N-4.77%

#### THE N-FORMYL KETO ESTER III

A solution of the acid II (0.120 g.) in dry ether (25 ml.) was treated with an excess of ethereal diazomethane and the mixture stirred at room temperature for one hour. Small amounts of polymer were then removed by filtration and the filtrate evaporated to dryness. The residual oil solidified on scratching.

Crystallization from ether yielded the pure ester III, m.p.  $117^\circ$ , which was sublimed for analysis. Infrared spectra showed maxima at 1732, 1710 and 1652  $\text{cm}^{-1}$  (nujol mull) and at 1738, 1715 and 1655  $\text{cm}^{-1}$  (chloroform).

Found C-66.13, 66.32%: H-8.11, 8.22%: O-20.87%: N-4.70%

$\text{C}_{17}\text{H}_{25}\text{O}_4\text{N}$  requires C-66.45%: H-8.14%: O-20.84%: N-4.56%

#### THE N-FORMYL HYDROXY ESTER IV

The keto ester III (0.262 g.) was refluxed for four hours with sodium borohydride (0.15 g.) in methanol (30 ml.). Most of the methanol was removed at the pump, the residues dissolved in dilute hydrochloric acid and the acidic solution extracted four times with chloroform, yielding a pale yellow solid (0.255 g.). Crystallization from ether afforded the pure ester IV, m.p.  $206^\circ$ , as colorless needles. The hydroxy ester showed infrared maxima at 3330, 1733 and 1635  $\text{cm}^{-1}$  (nujol) and at 3450, 1735 and 1648  $\text{cm}^{-1}$  (chloroform).

Found C-66.13, 66.31%: H-8.84, 8.73%: O-21.13%: N-4.40%

$\text{C}_{17}\text{H}_{27}\text{O}_4\text{N}$  requires C-66.02%: H-8.73%: O-20.71%: N-4.53%



THE N-FORMYL HYDROXY ACID V

The hydroxy ester IV (0.133 g.) was stirred at room temperature for eighteen hours in a 2% solution of sodium hydroxide in 50% ethanol (25 ml.). Most of the ethanol was removed at the pump, more water (25 ml.) added and the aqueous solution extracted six times with chloroform, giving a colorless solid (0.006 g.).

Acidification of the aqueous solution with dilute hydrochloric acid, followed by chloroform extraction, gave the pure hydroxy acid V (0.108 g.). Crystallization (four times) from ether afforded the analytical sample, m.p.  $211^{\circ}$ , which showed maxima in the infrared at 3450, 1698 and  $1603\text{ cm}^{-1}$  (nujol) and at 3670, 3500, 1732, 1648 and  $1612\text{ cm}^{-1}$  (chloroform).

Found C-65.01, 65.77%: H-8.50, 8.41%: O-22.26%: N-4.74%

$\text{C}_{16}\text{H}_{25}\text{O}_4\text{N}$  requires C-65.06%: H-8.53%: O-21.67%: N-4.74%

ATTEMPTED REDUCTION OF THE KETO ACID II WITH BOROHYDRIDE

The acid II (0.075 g.) was treated under conditions identical to those utilized above for the conversion III  $\rightarrow$  IV. The acidic product (0.068 g.) was found to be unchanged II. Prolonged refluxing of II with a large excess of sodium borohydride in methanol again led to the recovery of starting material.

THE N-METHYL DIOL XVII

The keto ester III (0.120 g.) was refluxed for twelve hours with lithium aluminum hydride (0.18 g.) in dry, freshly distilled tetrahydrofuran (30 ml.).

Water (0.18 ml.), 15% aqueous sodium hydroxide solution (0.18 ml.) and water (0.54 ml.) were added in turn (96), the resulting suspension filtered through anhydrous sodium sulphate and the solvent removed, leaving an almost colorless oil (0.099 g.).





The infrared spectrum of this oil which showed maxima at 3450 and 3650  $\text{cm}^{-1}$  and very little absorption between 1500 and 3000  $\text{cm}^{-1}$  indicated that virtually complete reduction had occurred, but the product was unstable and could not be obtained in a pure state either as the free base or as the hydrobromide or perchlorate salts.

#### HYDROLYSIS OF THE N-FORMYL KETO ESTER III

The keto ester III (0.105 g.) was refluxed for two and a half hours in 2N sulphuric acid (8 ml.). The solution was then cooled and liquid adhering to the condenser washed into the reaction flask with distilled water. The flask was then arranged for downward distillation and, adding water as required, a total of thirty-three fractions of ten ml. each were distilled. Each fraction was titrated with 0.0219N sodium hydroxide solution, using phenolphthalein indicator. A total of 7.460 ml. of the standard sodium hydroxide solution was used, equivalent to 49.1% of the theoretical monoacid.

The neutralized titration product was acidified with phosphoric acid and again steam distilled, a total of 285 ml. of distillate being collected. Titration of an aliquot with the standard base showed that the distillate was a  $4.77 \times 10^{-4}\text{N}$  acid solution.

Several standard solutions of formic acid, ranging from  $2 \times 10^{-4}\text{N}$  to  $4 \times 10^{-3}\text{N}$  were prepared. To each of the standard solutions and to the test solution (three samples) was separately added clean magnesium ribbon (80 mg.). The solutions were cooled to  $0^\circ$  and treated with concentrated hydrochloric acid (5 ml.) (The acid was added in ten portions of 0.05 ml. added at five



minute intervals.)

To each solution was then added 1.5 ml. of chromotropic acid reagent (prepared by dissolving chromotropic acid (0.6 g.) in 90% sulphuric acid (200 ml.)), and the solution heated on the steam bath for thirty minutes.

The white precipitate was removed by centrifugation and the visible spectrum of the blue supernatant liquids were studied.

The standard and test solutions all showed maxima at 380, 480 and 570  $m\mu$ , the 480  $m\mu$  peak being only half as intense as the other two.

The yellow acidic solution from the hydrolysis of III was continuously extracted with ether for three days, giving a pale yellow oil (0.069 g.) whose infrared spectrum showed maxima at 1720 and 1625  $\text{cm}^{-1}$  (chloroform) and no absorption at 1600  $\text{cm}^{-1}$  as expected. Treatment of the crude amino acid VI with ethereal diazomethane gave the corresponding methyl ester, whose infrared spectrum showed maxima at 1740, 1720 and 1620  $\text{cm}^{-1}$  (chloroform). The oily ester, however, defied attempts at purification.

#### HYDROLYSIS OF THE HYDROXY ESTER IV

The ester IV (0.190 g.) was refluxed for twenty-four hours in 2N sulphuric acid (8 ml.). Volatile acids were removed by steam distillation, a total of 100 ml. of distillate being collected. The distillate was reduced with magnesium (0.8 g.) and concentrated hydrochloric acid (5 ml.), the method used being identical to that described above.

The resulting solution was again steam distilled. The distillate was collected in 10 ml. fractions and each fraction separately treated with a solution of dimedone (0.1 g.) in 50%





ethanol (4 ml.). The mixtures were allowed to stand at room temperature overnight.

The first three fractions gave small crops of colorless needles, m.p. 184-187°. The infrared spectra of these crops were identical to that of the dimedone derivative of authentic formaldehyde (m.p. 192°). Melting point on admixture of the test and standard compounds showed no depression.

The amino acid VII from the hydrolysis was not investigated in detail.

#### OXIDATION OF LYCOPODINE TO THE LACTAM XXVI

The acetone used as solvent in this experiment was first purified by refluxing six hours with excess potassium permanganate. After distillation the acetone was dried over potassium carbonate and redistilled into the reaction flask.

Lycopodine (2.20 g.) in purified acetone was stirred at room temperature with potassium permanganate (3.52 g.) for four hours.

Most of the acetone was removed at the pump, the residues dissolved in dilute hydrochloric acid and this solution continuously extracted with ether for two days.

The ether extract was evaporated to dryness, the residues dissolved in dilute aqueous ammonia and again continuously extracted with ether for two days giving the pale yellow, solid, neutral products (1.03 g.).

Acidification of the aqueous layer, followed by continuous ether extractions, gave a small yield of acidic material (0.10 g.) which appeared to contain the N-formyl acid II.

The original aqueous solution was basified with ammonia and continuously extracted with ether to give unreacted lycopodine



(0.98 g.).

The neutral products were separated by chromatography over alumina (20 g.).

Elution with ether gave the pure lactam XXVI (0.56 g. - 24%) while chloroform elution gave a mixture (0.15 g.) which apparently contained further hydroxylated lactams, though these were not investigated.

The pure lactam melted at  $163^{\circ}$  after crystallization from ether and was found to be identical (m.p., m.m.p., infrared) to a sample of the  $\alpha$ -lactam kindly donated by Dr. MacLean. The lactam showed maxima in the infrared at  $1707$  and  $1630\text{ cm}^{-1}$  (chloroform),  $1710$  and  $1622\text{ cm}^{-1}$  (carbon tetrachloride) and  $1721$  and  $1655\text{ cm}^{-1}$  (nujol mull). In each case the two bands are attributed to the cyclic carbonyl and lactam group respectively. The analytical sample was prepared by sublimation of an extensively recrystallized sample.

Found C-72.83, 73.05%: H-8.84, 8.93%: O-12.64%: N-5.54%

$\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$  requires C-73.56%: H-8.84%: O-12.24%: N-5.36%

#### DIHYDROLYCOPODINE XXIX

##### (a) From lithium aluminum hydride reduction of lycopodine.

Lithium aluminum hydride (0.300 g.) was added in small portions to a stirred solution of lycopodine (1.095 g.) in anhydrous ether (50 ml.) and the mixture gently refluxed for four hours. Excess hydride was destroyed by adding, in turn, water (0.30 ml.), 15% aqueous sodium hydroxide (0.30 ml.) and water (0.90 ml.). The suspension was filtered, the residues washed with more ether and the combined organic solution dried over anhydrous magnesium sulphate, filtered and the solvent removed leaving a





colorless solid (1.1 g.), m.p. 166-168°.

Crystallization from ether yielded pure dihydrolycopodine XXIX (0.981 g.), m.p. 168-169°. The mother liquors from the crystallization were evaporated to dryness and the residues converted to the perchlorate in acetone. Crystallization from acetone-ether gave pure dihydrolycopodine perchlorate, m.p. 226° (0.138 g.). The total yield of XXIX was 98%.

(b) Sodium borohydride reduction of lycopodine.

Lycopodine (1.014 g.) was stirred at room temperature for thirteen hours with sodium borohydride (0.49 g.) in methanol (30 ml.).

More borohydride (0.92 g.) was then added and the mixture refluxed for a further two hours.

Most of the methanol was removed at the pump, aqueous sodium carbonate (50 ml.) added and the resulting solution extracted six times with chloroform, giving a colorless solid (0.996 g.).

Crystallization from ether gave pure dihydrolycopodine (0.698 g.). The mother liquors were evaporated to dryness and the residues converted to the perchlorate in methanol. Fractional crystallization from methanol-ether gave, in turn, lycopodine perchlorate (0.080 g.) and dihydrolycopodine perchlorate (0.118 g.). The mother liquors were reconverted to the free base, giving almost pure lycopodine (0.148 g.).

Total yield of dihydrolycopodine	77%
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Total recovered lycopodine	20%
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α-DIHYDROLYCOPODINE XXX

Lycopodine (0.760 g.) in methanol (40 ml.) was added to liquid ammonia (200 ml.) with vigorous stirring.



Lithium metal (0.9 g.) was added to this solution in small portions over a period of thirty minutes. The ammonia was allowed to evaporate, water (200 ml.) added and the aqueous solution extracted four times with chloroform to give a colorless glass (0.77 g.). Crystallization from ether gave pure  $\alpha$ -dihydrolycopodine **XXX** (0.626 g.) as colorless needles, m.p. 133.5°.

The mother liquors from the crystallization were evaporated to dryness to give a colorless oil, whose infrared spectrum indicated a mixture of **XXX** and unreacted lycopodine. The epimeric alcohol **XXIX** appeared to be absent. The oil was converted to the perchlorate in acetone and crystallized from acetone-ether to give  $\alpha$ -dihydrolycopodine perchlorate as colorless needles, m.p. 246° (0.11 g.).

The total yield of **XXX** was 91%.

#### Free base

Found C-76.93, 76.67%: H-11.00, 11.16%: O-7.29%: N-4.69%

C<sub>16</sub>H<sub>27</sub>ON requires C-77.06%: H-10.91%: O-6.42%: N-5.62%

#### Perchlorate

Found C-55.31, 55.46%: H-8.24, 8.31%: O-23.52%: N-4.44%

C<sub>16</sub>H<sub>27</sub>ON.HClO<sub>4</sub> requires C-54.94%: H-8.01%: O-22.89%: N-4.01%

#### THE OXIDATION OF **XXX** TO LYCOPODINE.

$\alpha$ -Dihydrolycopodine **XXX** (0.175 g.) was stirred at room temperature for forty-eight hours with chromium trioxide (0.2 g.) in glacial acetic acid (20 ml.). Most of the solvent was removed at the pump, the residues dissolved in aqueous ammonia and the solution extracted six times with ether yielding a colorless solid (0.166 g.), m.p. 107-110°.

Crystallization from n-pentane gave colorless crystals





(0.155 g.), identical (m.p., m.m.p., infrared) with a sample of authentic lycopodine.

#### LYCOPODANE XXXI

Sodium (0.100 g.) in freshly distilled diethylene glycol (40 ml.) was heated to  $180^{\circ}$  and anhydrous hydrazine distilled into the solution until refluxing occurred freely at  $180^{\circ}$ . The solution was then cooled and lycopodine (0.634 g.) quickly added. The mixture was then refluxed for seventeen hours. The temperature was then raised to  $210^{\circ}$  by distilling back some of the hydrazine into the hydrazine generator and the solution refluxed at this temperature for a further twenty-four hours.

Water (100 ml.) was added and the solution extracted six times with benzene. The combined organic extract was shaken twice with dilute hydrochloric acid, the latter basified with dilute aqueous ammonia and extracted four times with chloroform giving a pale yellow semisolid, which showed no carbonyl absorption in the infrared.

Conversion to the perchlorate in acetone, followed by crystallization from ethanol-ether or, better, from water gave lycopodane perchlorate XXXI.HClO<sub>4</sub>, as colorless needles, m.p.  $225^{\circ}$ .

The corresponding methiodide crystallized from ethanol-ether melted at  $288^{\circ}$ .

The free base could not be crystallized.

#### Perchlorate

Found C-57.38, 57.32%: H-8.38, 8.12%: O-19.25%: N-4.71%

C<sub>16</sub>H<sub>27</sub>N.HClO<sub>4</sub> requires C-57.56%: H-8.45%: O-19.17%: N-4.71%

#### Methiodide

Found C-54.95%: H-8.12%: N-3.47%: I-33.06%

C<sub>17</sub>H<sub>30</sub>NI requires C-54.40%: H-8.06%: N-3.73%: I-33.81%



DIHYDROLYCOPODINE ACETATE XXXIII

Dihydrolycopodine XXIX (1.002 g.) was allowed to stand at room temperature for seventeen hours in a mixture of acetic anhydride (35 ml.) and pyridine (35 ml.). The solution was then heated on the steam bath for two hours, cooled, most of the solvents removed at the pump and the residues dissolved in dilute aqueous ammonia. Extraction with chloroform gave a deep yellow oil. Chromatography over alumina (30 g.) gave, with benzene eluent, a colorless oil (0.875 g.) which slowly solidified on standing. Sublimation gave the pure acetoxy compound XXXIII, m.p. 96-98°, which showed maxima in the infrared at 1738  $\text{cm}^{-1}$  (nujol) and at 1740  $\text{cm}^{-1}$  (in carbon tetrachloride).

The perchlorate, m.p. 230°, from acetone-ether, showed maximal absorption at 1685  $\text{cm}^{-1}$  (nujol), while the hydrobromide, m.p. 259-262°, absorbed at 1732  $\text{cm}^{-1}$  (nujol).

$\alpha$ -DIHYDROLYCOPODINE ACETATE XXXII

$\alpha$ -Dihydrolycopodine XXX (0.251 g.) was stirred at room temperature for twenty-three hours with acetic anhydride (12 ml.) and pyridine (12 ml.). Most of the solvents were removed at the pump, aqueous sodium bicarbonate added and the resulting solution extracted four times with chloroform, giving a light brown oil (0.276 g.). This oil could not be crystallized directly, although the infrared spectra which in carbon tetrachloride showed an intense maximum at 1740  $\text{cm}^{-1}$  and no hydroxyl absorption indicated that acylation was virtually complete.

Purification was readily accomplished by conversion to the perchlorate in acetone, followed by crystallization from acetone-ether. The perchlorate of XXXII, m.p. 276-278°, showed a maximum





in the infrared at  $1732\text{ cm}^{-1}$  (nujol mull).

Found C-55.17, 55.16%; H-7.68, 7.66%; O-25.24%; N-4.15%

$\text{C}_{18}\text{H}_{29}\text{O}_2\text{N} \cdot \text{HClO}_4$  requires C-55.24%; H-7.67%; O-24.53%; N-3.58%

The free base which melted at  $76-78^\circ$  after sublimation could not be obtained in a crystalline form.

Treatment of the epimeric alcohol XXIX under identical conditions led only to partial acetylation. The infrared spectrum of the crude product (in carbon tetrachloride) showed maxima at  $1740\text{ cm}^{-1}$  (acetoxo group) but also strong hydroxyl absorption.

#### THE CATHYLATE XXXIV

Ethyl chloroformate (1 ml.) was added to a stirred solution of  $\alpha$ -dihydrolycopodine XXX (0.108 g.) in dry pyridine (4 ml.) and the solution which immediately turned yellow was stirred at room temperature for two hours. Most of the solvent was removed at the pump, the residues dissolved in aqueous ammonia and extracted four times with chloroform, giving a pale yellow ether soluble oil (0.098 g.).

The infrared spectrum of the crude product (in carbon tetrachloride) indicated that almost complete cathylation had occurred (intense maximum at  $1743\text{ cm}^{-1}$  and very little hydroxyl absorption). However, attempted perchlorate formation in acetone yielded only the perchlorate of  $\alpha$ -dihydrolycopodine indicating that the cathylate is readily hydrolyzed by perchloric acid. The cathylate methiodide was readily formed by treatment of the crude reaction product with excess methyl iodide in refluxing acetone. After crystallization from acetone-ether the methiodide melted at  $233^\circ$  and showed a maximum in the infrared at  $1732\text{ cm}^{-1}$ .



Found C-51.97, 52.26%: H-7.41, 7.57%: O-11.71%

$C_{20}H_{34}O_3NI$  requires C-51.82%: H-7.40%: O-10.36%

Treatment of the epimeric alcohol XXIX under identical conditions led only to the recovery of starting material.

ANHYDRODIHYDROLYCOPODINE XXXV

(a) By phosphorus pentachloride dehydration of XXIX.

Dihydrolycopodine XXIX (0.245 g.) was refluxed for six hours with phosphorus pentachloride (0.50 g.) in freshly distilled xylene (30 ml.). The mixture was cooled and shaken with water (20 ml.). The aqueous layer was removed and the xylene layer shaken twice with 20 ml. portions of dilute hydrochloric acid. The combined aqueous solutions were extracted once with ether, basified with aqueous ammonia and extracted four times with chloroform to give a dark brown oil (0.183 g.).

Distillation of the oil at 0.1 mm Hg yielded a colorless oil which was converted to a crystalline perchlorate (45 mg., m.p.  $236^\circ$ ) in acetone-ether. The infrared spectrum (nujol) of this perchlorate showed no hydroxyl or carbonyl absorption as expected.

(b) By phosphorus oxychloride dehydration of XXIX.

Phosphorus oxychloride (1.5 ml.) was added to a stirred solution of dihydrolycopodine (0.702 g.) in dry pyridine (20 ml.). The solution turned deep blue immediately, then wine red, then slowly brown. The mixture was heated on the steam bath for one hour, then stirred at room temperature overnight. Most of the pyridine was removed at the pump, the residues dissolved in aqueous ammonia and the basic solution extracted six times with chloroform to give an ether soluble labile oil whose infrared spectrum showed no hydroxyl absorption.





The crude product was converted to the perchlorate in acetone and crystallized from acetone-ether or, better, from water, to give pure anhydrodihydrolycopodine perchlorate, XXXV.HClO<sub>4</sub>, (0.746 g., 78%), m.p. 238-239°.

The Nuclear Magnetic Resonance (NMR) spectrum of the oily free base (in chloroform) exhibited peaks at 4.26 $\tau$  (one-proton singlet, attributed to R<sub>2</sub>C=CH $\underline{R}$ ) and at 9.04 $\tau$  (three-proton doublet, J=5.5 c.p.s., attributed to R<sub>2</sub>CH-CH $\underline{3}$ .)

#### THE CHLORO COMPOUND XXVI

$\alpha$ -Dihydrolycopodine XXX (0.564 g.) was heated on the steam bath for one hour with phosphorus oxychloride (1.5 ml.) in dry pyridine (20 ml.). After standing at room temperature overnight most of the pyridine was removed at the pump, aqueous ammonia added and the solution extracted four times with chloroform to give a light brown, ether soluble semisolid (0.434 g.).

Conversion to the perchlorate in acetone, followed by crystallization from acetone-ether gave pure 5-chloro-dihydrodeoxylycopodine XXXVI.HClO<sub>4</sub> (0.444 g.), m.p. 230-231°.

Found C-52.47, 52.22%: H-7.19, 7.36%: O-17.12%: N-3.88%:

Cl-19.07, 19.11%

C<sub>16</sub>H<sub>26</sub>NC1.HClO<sub>4</sub> requires C-52.18%: H-7.39%: O-17.38%:

N-3.80%: Cl-19.25%

The free base which could not readily be crystallized melted at 92-94° after sublimation.

#### ATTEMPTED HYDROGENATION OF XXXV.HClO<sub>4</sub>

Attempted reduction of anhydrodihydrolycopodine perchlorate under the conditions indicated below led only to the recovery of starting material.



<u>SOLVENT</u>	<u>CATALYST</u>	<u>HYDROGEN PRESSURE</u>	<u>TIME</u>
AcOH	Pd/C	Atmospheric	24 hours
AcOH	Rh/Al <sub>2</sub> O <sub>3</sub>	50 lbs p.s.i.	48 hours
AcOH	Rh/Al <sub>2</sub> O <sub>3</sub>	750 lbs p.s.i.	24 hours

#### THE BORON COMPOUND XXXVII

Anhydrodihydrolycopodine XXXV (0.505 g.) in dry ether (40 ml.) was treated with a solution of boron trifluoride etherate (1.84 g.) in dry ether (10 ml.) and the mixture stirred at room temperature for five minutes.

Lithium aluminum hydride (0.75 g.) was added in small portions over a period of thirty minutes and the mixture stirred at room temperature for a further eighteen hours.

Acetone (1 ml.) was cautiously added, followed by water (1 ml.), the solution dried with anhydrous magnesium sulphate, filtered and the solvent removed leaving a colorless semisolid (0.496 g.).

Crystallization from n-hexane afforded the pure boron compound as long colorless needles (0.438 g., 81%), m.p. 143-144°. Sublimation gave the analytical sample.

Found C-79.08, 78.83%: H-11.16, 11.26%: N-5.61%: B-4.05%

C<sub>16</sub>H<sub>25</sub>N.BH<sub>3</sub> requires C-78.37%: H-11.52%: N-5.72%: B-4.41%

The infrared spectrum of XXXVII (nujol mull) showed maxima at 2360, 2325 and 2275 cm<sup>-1</sup> attributed to B-H and at 822 and 812 cm<sup>-1</sup> attributed to the olefinic linkage.

#### THE REACTION OF THE BORON COMPOUND XXXVII WITH BASIC PEROXIDE

The boron compound XXXVII (0.325 g.) was dissolved in 90% ethanol (20 ml.) containing sodium hydroxide (0.2 g.) and the solution heated to 40°. Hydrogen peroxide (2 ml., 30%) was added





dropwise and the mixture gently refluxed for a further fifteen minutes.

Water (50 ml.) was added and the solution extracted four times with chloroform to give a colorless oil (0.301 g.). The infrared spectrum of this material was very similar to that of anhydrodihydrolycopodine, although small peaks at 2480, 2330, 2280 and  $1180\text{ cm}^{-1}$  suggested that some of the boron compound remained.

The oil was therefore again treated with hydrogen peroxide in ethanolic sodium hydroxide with refluxing for thirty minutes. The reaction mixture was worked up as before to give a colorless oil (0.3 g.) whose infrared spectrum (in carbon tetrachloride) showed poorly defined peaks at 3290 and  $3220\text{ cm}^{-1}$ , although the spectrum was again very similar to that of anhydrodihydrolycopodine.

Crystallization from ether gave small colorless needles, all with the same infrared spectrum (nujol) but existing in two crystalline forms, m.ps.  $61^{\circ}$  and  $105-107^{\circ}$ , both with maxima at 3395 and  $3215\text{ cm}^{-1}$ .

Both forms gave the same perchlorate which after crystallization from acetone-ether melted at  $213-215^{\circ}$ . This perchlorate XXXVIII. $\text{HClO}_4$  showed no absorption in the infrared between 1520 and  $2500\text{ cm}^{-1}$ .

Found C-55.58, 55.66%: H-7.73, 7.55%: O-24.17%: N-3.76%

$\text{C}_{16}\text{H}_{25}\text{ON}.\text{HClO}_4$  requires C-55.25%: H-7.53%: O-23.00%: N-4.03%

No attempt was made to isolate pure anhydrodihydrolycopodine from the reaction product, although its presence was indicated from the infrared spectra.

#### REACTION OF THE BORON COMPOUND XXXVII WITH BASE

The boron compound (0.420 g.) was refluxed for thirty minutes



in 90% ethanol containing sodium hydroxide (0.5 g.). The reaction mixture was worked up in the same manner as before to give a colorless oil whose infrared spectrum was almost identical to that of anhydrodihydrolycopodine. The spectrum did not show the maxima at 3395 and 3215  $\text{cm}^{-1}$  attributed above to the N-oxide.

The oily product was dissolved in acetone and the solution neutralized with perchloric acid. The addition of ether led to precipitation of crystals, identical in all respects (m.p., m.m.p., infrared) to an authentic sample of anhydrodihydrolycopodine perchlorate.

#### PYROLYSIS OF THE ACETATES XXXII AND XXXIII

In all cases the infrared spectrum of the crude product was examined without further purification.

##### (a) O-Acetyldihydrolycopodine XXXIII

CONDITIONS	<u>PRODUCT</u>
Vacuum distillation at 130°.	Pure XXXIII
Sample heated for ten minutes at atmospheric pressure at 200° then vacuum distilled.	Pure XXXIII
Sample heated for three hours in evacuated sealed tube at 400° then vacuum distilled.	Crude XXXIII
Sample passed through evacuated tube containing glass beads heated to 400°.	Pure XXXIII
Sample heated for three hours at 520° in an evacuated tube containing glass beads.	Crude XXXIII

##### (b) O-Acetyldihydrolycopodine XXXII

Conditions identical to those used above again led mainly to the recovery of starting material. The failure of the acetates to eliminate readily led to the abandonment of the reaction.





THE XANTHATE METHIODIDE XXXIX

$\alpha$ -Dihydrolycopodine XXX (0.480 g.) in dry ether (50 ml.) was refluxed for sixty hours with sodium metal (0.060 g.). Carbon disulphide (1 ml.) was then added and refluxing continued for a further twenty-four hours. Excess methyl iodide was added to the yellow suspension and the mixture again refluxed for twenty-four hours resulting in a white suspension in a pale yellow liquid.

The suspension was removed by filtration and crystallized from 98% ethanol to give the pure xanthate methiodide (0.545 g.), m.p. 280-282° (decomposition). The infrared spectrum of XXXIX showed intense maxima at 1235, 1220 and 927  $\text{cm}^{-1}$  (nujol).

Found C-47.49, 47.69%: H-6.85, 6.66%: N-3.07%: S-13.22%:  
I-26.41%

$\text{C}_{18}\text{H}_{29}\text{OS}_2\cdot\text{CH}_3\text{I}$  requires C-47.39%: H-6.70%: N-2.91%:  
S-13.32%: I-26.36%

PYROLYSIS OF THE XANTHATE METHIODIDE XXXIX

The xanthate methiodide XXXIX (0.115 g.) was heated at 265° at atmospheric pressure for twenty minutes. After this time the material was completely liquified. The oil was cooled and distilled at 140°/0.1 mm Hg to give a colorless oil (41 mg.) which was dissolved in a small volume of acetone and neutralized with 70% perchloric acid. Addition of ether gave a colorless precipitate (47 mg.) which, after one recrystallization from acetone-ether, melted at 238-239°. This perchlorate was found to identical (m.p., m.m.p., infrared) to the perchlorate of anhydrodihydrolycopodine XXXV.

THE REDUCTION OF THE LACTAM XXVI

(a) Lithium aluminum hydride reduction



(i) Limited reducing agent

The lactam XXVI (49 mg.) in dry ether (25 ml.) was gently refluxed for one hour with lithium aluminum hydride (10 mg.). Water (30 ml.) was cautiously added and the ether layer removed. The aqueous layer was shaken twice with chloroform and the combined organic extracts dried over anhydrous magnesium sulphate, filtered and the solvent removed leaving a pale yellow oil (48 mg.).

Chromatography over alumina (2 g.) gave, with ether eluent, the keto-lactam XXVI (21 mg.) while chloroform eluent gave the pure hydroxy-lactam XLI (26 mg.).

The hydroxy-lactam XLI was purified by crystallization from a small volume of acetone and sublimed for analysis. The pure compound, m.p. 189-190° showed maxima in the infrared at 3500, 3420 and 1610  $\text{cm}^{-1}$ .

Found C-72.56, 72.62%; H-9.37, 9.44%; O-12.52%

$\text{C}_{16}\text{H}_{25}\text{O}_2\text{N}$  requires C-72.96%; H-9.57%; O-12.15%

In a second experiment with more lithium aluminum hydride a mixture of dihydrolycopodine XXIX and the hydroxy lactam XLI was obtained.

(ii) Excess reducting agent

Lithium aluminum hydride (0.075 g.) was added to a stirred solution of the lactam XXVI (0.051 g.) in purified tetrahydrofuran (25 ml.) and the mixture gently refluxed for four hours. Wet tetrahydrofuran was added and the suspension filtered. The residues were dissolved in water and extracted twice with chloroform. The combined organic solutions were dried over anhydrous magnesium sulphate, filtered and the solvent removed, leaving a yellow oil (0.046 g.). Chromatography over alumina (3 g.) with





chloroform eluent gave a colorless solid (0.035 g.), identical (m.p., m.m.p., infrared) with an authentic sample of dihydrolycopolodine XXIX.

(b) Sodium borohydride reduction

The lactam XXVI (0.913 g.) was refluxed for sixteen hours with sodium borohydride (2.0 g.) in 99% methanol containing sodium hydroxide (0.4 g.). Most of the methanol was removed at the pump, the residues dissolved in dilute hydrochloric acid and the aqueous solution extracted three times with chloroform to give a pale yellow semisolid.

Chromatography over alumina (20 g.) with chloroform eluent yielded a colorless foam (0.9 g.) which showed no ketonic carbonyl absorption in the infrared. Crystallization from acetone furnished the pure hydroxy-lactam XLI (0.805 g.), m.p. 189-190°.

(c) Lithium-liquid ammonia reduction

The lactam XXVI (0.109 g.) in methanol (10 ml.) was carefully added to liquid ammonia (200 ml.) with vigorous stirring. Lithium metal (0.2 g.) was added in small portions over a period of thirty minutes and the ammonia allowed to evaporate.

Water (50 ml.) was added and the aqueous solution extracted five times with chloroform to give an almost colorless solid (0.103 g.) which showed no ketonic carbonyl absorption in the infrared.

Crystallization from acetone furnished the pure  $\alpha$ -dihydro lactam XLII, as colorless rosettes, m.p. 252-253°. The analytical sample obtained by sublimation of the crystalline material showed maxima in the infrared at 3350 and 1612  $\text{cm}^{-1}$  (nujol) and at 3625, 3400 and 1613  $\text{cm}^{-1}$  (in chloroform).



Found C-72.77%: H-9.99%: O-11.53%: N-5.71%

C<sub>16</sub>H<sub>25</sub>O<sub>2</sub>N requires C-72.96%: H-9.57%: O-12.15%: N-5.32%

#### THE ANHYDRODIHYDROLACTAM XLIII

The dihydrolactam XL (0.155 g.) was stirred at room temperature for twelve hours with phosphorus oxychloride (2 ml.) in pyridine (50 ml.). The solution was then poured into ice-cold dilute hydrochloric acid and extracted four times with chloroform to give a light brown oil (0.12 g.).

Chromatography on alumina (3 g.) with ether eluent gave a colorless oil (0.097 g.) whose infrared spectrum showed no hydroxyl absorption. Crystallization from n-hexane afforded the anhydro compound XLIII, m.p. 115° which was sublimed for analysis.

Found C-78.08%, 78.23%: H-9.67, 9.62%: O-6.75%: N-5.78%

C<sub>16</sub>H<sub>23</sub>ON requires C-78.32%: H-9.42%: O-6.52%: N-5.71%

The infrared spectrum of XLIII showed maxima at 1640 and 818 cm<sup>-1</sup> (nujol mull) attributed to amide and olefinic double bond respectively.

#### THE XANTHATE XLIV

α-Dihydrolactam XLI (0.037 g.) was refluxed with sodium metal (0.015 g.) in dry ether (15 ml.) for sixteen hours. Carbon disulphide (1 ml.) was then added and refluxing continued for three hours. Methyl iodide (2 ml.) was added and the mixture refluxed for a further forty-eight hours.

The yellow suspension was filtered, the residues washed with a little chloroform and the combined filtrates evaporated to dryness leaving a pale yellow solid. Crystallization from n-hexane afforded the pure colorless xanthate XLIV, m.p. 154-155°, which showed maxima in the infrared at 1642, 1245, 1218 and 1048 cm<sup>-1</sup>.





Found C-61.37, 61.45%: H-8.23, 8.46%: O-9.22%: N-4.01%

$C_{18}H_{27}O_2S_2N$  requires C-61.15%: H-7.70%: O-9.05%: N-3.96%

#### PYROLYSIS OF THE XANTHATE XLIV

The xanthate XLIV (0.030 g.) was heated for two minutes at  $200^\circ$  at atmospheric pressure, cooled and distilled at  $140^\circ/0.1$  mm Hg to give a colorless solid, m.p.  $112-114^\circ$ . Crystallization from n-hexane gave small colorless plates, m.p.  $117-118^\circ$ . The mixed melting point with the dehydration product above was  $115.5-117^\circ$ .

The infrared and NMR spectra of the pyrolysis and dehydration products were very similar but not identical. In both cases the NMR showed doublets at 9.097 (J=5 c.p.s.) attributed to  $-\underline{CH}-\underline{CH}_3$  and peaks in the olefinic proton region at 4.60 and 4.477, although the relative intensities of these two peaks were different.

#### THE 5,15 ETHER LIV

Lead tetraacetate (0.20 g.) was added to a solution of the hydroxy-lactam XLI (0.051 g.) in dry benzene and the mixture refluxed for sixteen hours. Water (20 ml.) was then added, resulting in two almost colorless layers. The aqueous layer was extracted twice more with chloroform, the combined organic extracts dried over anhydrous sodium sulphate, filtered and the solvent removed leaving an almost colorless semisolid (0.057 g.).

Crystallization from n-hexane furnished the pure ether XLVIII, m.p.  $178-180^\circ$ , (0.041 g., 80%) which was sublimed for analysis.

Found C-73.46, 73.66%: H-9.27, 9.02%: N-4.98%

$C_{16}H_{23}O_2N$  requires C-73.56%: H-8.84%: N-5.36%

The mass spectrum of XLVIII showed that the molecular weight was



in fact 261 and the infrared spectrum showed amide absorption at  $1620\text{ cm}^{-1}$  (nujol) with no other carbonyl or hydroxyl peaks as expected.

The NMR (in deutero chloroform) showed peaks at  $8.78\tau$  (singlet, 3H, attributed to  $\begin{array}{c} \text{C} \diagup \text{C} \diagdown \\ \text{C} \diagdown \text{C} \diagup \\ \text{O}- \end{array} \text{CH}_3$ ),  $5.47\tau$  (one-proton doublet ( $J=16\text{ c.p.s.}$ ) attributed to the deshielded 1-equatorial proton) and at  $6.33\tau$  (broadened singlet, width at half height about  $8\text{ c.p.s.}$ , attributed to the 5-equatorial proton).

#### ISOLATION OF THE ALKALOIDS OF LYCOPODIUM CLAVATUM var. MEGASTACHYON

Dried, powdered L. Clavatum var. megastachyon (15.5 kg.) was Soxhlet-extracted for twenty-four hours with methanol. Most of the methanol was removed by distillation and the residue treated with ice-cold 1% aqueous hydrochloric acid (5 l.). The acidic solution was filtered (Celite) from insoluble material which was then vigorously stirred with cold 1% hydrochloric acid (5 l.) for several hours and the mixture again filtered. The combined acid solutions were basified with ice-cold dilute aqueous ammonia and extracted five times with chloroform. The chloroform was removed by distillation and the oily residue dissolved in ice-cold 1% hydrochloric acid (5 l.) and washed three times with ether to remove neutral material. The aqueous solution was then basified with ice-cold aqueous ammonia and extracted four times with chloroform. Evaporation of the dried chloroform extracts left 18.2 g. of basic material as a dark brown gum.

#### SEPARATION AND PURIFICATION OF THE ALKALOIDS

The crude alkaloid was placed on a column of alumina (1 lb.) in ether and eluted in four fractions:





Fraction A: colorless oil (9.01 g.) eluted with ether (3 l.)

Fraction B: colorless oil (1.88 g.) eluted with ether (6 l.)

Fraction C: light brown foam (8.50 g.) eluted with chloroform (6 l.).

Fraction D: dark oil (3.32 g.) eluted with methanol (1 l.)

Fraction B was crystallized from acetone to give the dihydro-lycopodine-flabelliformine complex, m.p. 213-214° (0.3 g.).

Found C-74.78%: H-10.16%: O-9.82%: N-5.44%

C<sub>32</sub>H<sub>52</sub>O<sub>3</sub>N<sub>2</sub> requires C-75.00%: H-10.16%: O-9.37%: N-5.47%

The infrared spectrum of the complex showed maxima (nujol) at 2600-3300 (broad OH superimposed on C-H) and 1710 cm<sup>-1</sup> (ketone).

Fraction C crystallized from acetone to give clavolonine (1.53 g.), m.p. 233-234°, identical with an authentic sample furnished by Dr. R. H. Burnell.

Fraction D was chromatographed over alumina and yielded further clavolonine (0.50 g.) when eluted with chloroform. Elution with chloroform-methanol (99:1) and crystallization from methanol-ether yielded "diol I" (0.070 g.) m.p. 261-263°.

Found C-72.36, 72.49%: H-9.36, 9.58%: N-5.60%

C<sub>16</sub>H<sub>25</sub>O<sub>2</sub>N requires C-72.96%: H-9.57%: N-5.32%

The infrared spectrum of "diol I" showed a maximum (nujol) at 3400 cm<sup>-1</sup> (strong -OH absorption) but no carbonyl absorption.

Fraction A and the residues from fractions B and C were combined and carefully chromatographed over alumina (1 lb.). Elution with benzene (5 l.) yielded lycopodine (5.36 g.), identical with an authentic sample. Elution with ether (5 l.) and crystallization from n-hexane gave acetyllycoclavine m.p. 144-145°, (2.03 g.).



Found C-68.74, 68.54%: H-8.69, 9.15%: O-19.03%: N-3.55%

$C_{20}H_{31}O_4N$  requires C-68.74%: H-8.94%: O-18.31%: N-4.01%

The infrared spectrum of the alkaloid showed maxima at 1745 and 1225  $cm^{-1}$  ( $OCOCH_3$ ) (in carbon tetrachloride) and at 1740, 1725, 1250 and 1238  $cm^{-1}$  (nujol). Elution with chloroform and crystallization of the eluates from acetone yielded lycoclavine (1.32 g.). The analytical sample, m.p. 212-213°,  $[\alpha]_D -9^\circ$ , (95% ethanol) was prepared by several recrystallizations from acetone.

Found C-70.11, 70.19%: H-9.43, 9.48%: O-15.71%: N-4.57%

$C_{18}H_{29}O_3N$  requires C-70.32%: H-9.51%: O-15.57%: N-4.54%

Lycoclavine,  $pK_a$  (50% methanol) 9.6, shows maxima in the infrared (in carbon tetrachloride) at 3620 (shoulder), 3600, 1736 and 1240  $cm^{-1}$  and (in nujol) at 3160, 1732, 1248 and 1236  $cm^{-1}$ . The methiodide melted at 314°, the perchlorate at 283-286° and the hydrochloride at 281-285°.

The mother liquors from the crystallizations of acetyllycoclavine were evaporated to dryness and the residues dissolved in acetone. Neutralization with 70% perchloric acid followed by the addition of ether gave a small yield of a crystalline perchlorate, m.p. 230°, with a maximum in the infrared at 1685  $cm^{-1}$  (nujol). This material was identical with an authentic sample of O-acetyl dihydrolycopodine perchlorate.

Further small quantities of crystalline material could be obtained by chromatography of the mother liquors from the above operations, but the latter were not studied in detail.

PROOF OF THE COMPOSITION OF THE MOLECULAR COMPLEX m.p. 213-214°

Dihydrolycopodine (10.6 mg.) and flabelliformine (11.2 mg.) were combined in hot acetone. The solution deposited colorless





crystals (15.2 mg.), m.p. 204-206°, on cooling. The infrared spectrum (nujol) was identical to that of the material isolated from the plant, and the mixed melting point (206-210°) showed no depression.

Oxidation of the complex (26) with chromium trioxide-pyridine and alumina chromatography of the resulting product yielded lycopodine (eluted with benzene) and flabelliformine (eluted with ether).

DESACETYLLYCOCLAVINE (LXVII,  $R=R'=H$ )

(a) By alkaline hydrolysis of lycoclavine.

Lycoclavine (0.109 g.) was refluxed for one hour with a 2% solution of sodium hydroxide in 80% methanol (25 ml.). Most of the methanol was removed at the pump, water (30 ml.) added and the aqueous solution extracted four times with chloroform to give a colorless foam (0.091 g.) whose infrared spectrum showed no carbonyl absorption. Crystallization from a small volume of acetone yielded elongated prisms (40 mg.), m.p. 207-208°. The diol was difficult to crystallize in good yield and was sublimed for analysis.

Found C-72.28, 72.48%; H-10.30, 10.34%; N-5.45%

$C_{16}H_{27}O_2N$  requires C-72.41%; H-10.25%; N-5.28%

The infrared spectrum of desacetyllycoclavine showed concentration independent bands at  $3620\text{ cm}^{-1}$  (in carbon tetrachloride) and at  $3618\text{ cm}^{-1}$  (in chloroform).

The perchlorate, prepared by neutralizing an acetone solution of the base with 70% perchloric acid and crystallization from either acetone-ether or methanol-ether was found to exist in two crystalline forms, one melting at 230-238°, the other at 276-278°.



The two forms have different infrared spectra (nujol mulls), but are readily interconverted by seeding.

(b) By lithium aluminum hydride reduction of lycoclavine.

Lycoclavine (0.022 g.) in dry ether (20 ml.) was refluxed for two and a half hours with lithium aluminum hydride (0.008 g.). Excess hydride was destroyed by adding moist ether, the solution shaken once with aqueous sodium hydroxide and the aqueous extract extracted twice with chloroform. The combined organic solutions were dried over anhydrous magnesium sulphate, filtered and the solvent removed, leaving a colorless oil, which, after distillation, furnished the pure diol desacetyllycoclavine (LXVII,  $R=R'=H$ ), (0.016 g.).

(c) By lithium aluminum hydride reduction of acetyllycoclavine.

Acetyllycoclavine (LXVII,  $R=R'=Ac$ ) (0.202 g.) in dry ether (50 ml.) was refluxed with lithium aluminum hydride (0.250 g.) for two and a half hours. Excess hydride was destroyed by adding, in turn, water (0.25 ml.), 15% aqueous sodium hydroxide (0.25 ml.) and water (0.75 ml.) (96). The suspension was filtered, the residues washed with chloroform and the combined filtrates dried over anhydrous magnesium sulphate, filtered and the solvent evaporated, leaving a colorless solid. Sublimation furnished the pure diol, desacetyllycoclavine (LXVII,  $R=R'=H$ ) (0.148 g.), m.p. 203-206°, identical with that obtained above.

(d) By alkaline hydrolysis of acetyllycoclavine.

Acetyllycoclavine (0.062 g.) was stirred at room temperature in 0.9% ethanolic potassium hydroxide (20 ml.) for twenty-four hours. Most of the ethanol was removed at the pump, water added and the aqueous solution extracted continuously with ether for twenty





hours, giving a colorless oil which, on distillation, gave the pure diol, desacetyllycoclavine (0.022 g.).

(e) By acid hydrolysis of acetyllycoclavine.

Acetyllycoclavine (0.060 g.) was refluxed for sixteen hours in 20% aqueous hydrochloric acid (30 ml.). The solution was then neutralized with sodium bicarbonate and continuously extracted with ether to give a colorless solid, which on sublimation afforded desacetyllycoclavine (0.032 g.), m.p. 203-206°.

(f) By lithium aluminum hydride reduction of Alkaloid L.20.

Alkaloid L.20 (LXXV, R=H) (0.038 g.) was added to a slurry of lithium aluminum hydride (0.102 g.) in dry ether (50 ml.) and the mixture refluxed for twelve hours. Water (0.10 ml.), 15% aqueous sodium hydroxide (0.10 ml.) and water (0.30 ml.) were added in turn (96), the suspension filtered through anhydrous sodium sulphate and the residues washed well with chloroform. The combined filtrates were evaporated to dryness, and the residual colorless semisolid sublimed to give a colorless solid (0.032 g.), m.p. 191-196°, whose infrared spectrum was virtually identical to that of authentic desacetyllycoclavine. The perchlorate of the sublimed material, prepared by neutralizing an acetone solution of the material with 70% perchloric acid and crystallizing the product from acetone-ether, was identical in all respects (m.p., m.m.p., infrared) to the perchlorate of desacetyllycoclavine.

ACETYLATION OF LYCOCLAVINE

Lycoclavine (0.087 g.) was kept for eighteen hours in a mixture of acetic anhydride (4 ml.) and pyridine (2 ml.). The solution was then diluted with chloroform and shaken with ice-cold dilute



ammonium hydroxide. The chloroform layer was separated, washed with water, dried and evaporated. The off-white solid remaining was chromatographed on alumina (5 g.). Elution with ether yielded a colorless solid (0.086 g.). Crystallization from n-hexane gave acetyllcoclavine, m.p. 144-145°, identical in all respects to the naturally occurring compound described above.

#### ACETYLATION OF DESACETYLLYCOCLAVINE

Desacetyllcoclavine (0.106 g.) was stirred at room temperature for twenty hours in a mixture of acetic anhydride (5 ml.) and pyridine (3 ml.). Most of the solvents were removed at the pump at room temperature, the residues dissolved in methylene chloride (1 ml.) and chromatographed on alumina (5 g.) with methylene chloride eluent to give a colorless solid (0.125 g.) whose infrared spectrum was virtually identical to that of acetyllcoclavine. Crystallization (once) from n-hexane gave the pure di-acetate, identical in all respects (m.p., m.m.p., infrared) to an authentic sample of acetyllcoclavine.

#### LYCOCLAVINE FROM ACETYLLYCOCLAVINE

Acetyllcoclavine (0.866 g.) was refluxed for one and a half hours with 10% aqueous hydrochloric acid, then the solution was neutralized with sodium bicarbonate and continuously extracted with ether. Evaporation of the dried ether extract and crystallization of the residue from acetone gave lycoclavine (0.713 g.), m.p. 211-213°, identical (m.m.p., infrared) to the natural material.

#### "LYCOCLAVINONE"(LXIX, R=Ac)

Lycoclavine (0.068 g.) was dissolved in 98% acetic acid (20 ml.) containing chromium trioxide (0.70 g.) and the resulting





solution kept at room temperature for eighteen hours, then made basic with cold dilute ammonium hydroxide and extracted six times with chloroform. Evaporation of the dried chloroform solution gave a colorless semisolid (0.069 g.) which was chromatographed over alumina (5 g.). Elution with ether gave "lycoclavinone" (0.040 g.). Elution with chloroform yielded unreacted lycoclavine (0.015 g.).

Lycoclavinone, after recrystallization from Skellysolve B, melted at 174-175° and was sublimed for analysis.

Found C-70.39, 70.64%: H-9.11, 9.06%: O-15.73%

C<sub>18</sub>H<sub>27</sub>O<sub>3</sub>N requires C-70.79%: H-8.92%: O-15.72%

The acetoxy ketone showed maxima in the infrared at 1751, 1245 cm<sup>-1</sup> (OCOCH<sub>3</sub>) and 1724 cm<sup>-1</sup> (ketone) (in carbon tetrachloride), and at 1737, 1231 and 1218 cm<sup>-1</sup> (OCOCH<sub>3</sub>) and 1704 cm<sup>-1</sup> (ketone) (nujol mull). The ultraviolet spectrum showed absorption at 282 mμ (log ε=2.56). The optical rotatory dispersion (ORD) curve showed a positive Cotton effect (c 0.023) [α]<sub>400</sub> +290°, [α]<sub>308</sub> +8,300°, [α]<sub>271</sub> -15,400°, [α]<sub>260</sub> -7,500°. Finally, the NMR spectrum showed peaks at 9.17τ (doublet, J=5.5 c.p.s.) attributed to CHCH<sub>3</sub>, 7.83τ, singlet (OCOCH<sub>3</sub>) and 4.60τ (doublet, J=5.5 c.p.s.) attributed to the C-6 proton. The perchlorate of "lycoclavinone" (LXIX, R=Ac) melted at 283-285° after crystallization from acetone-ether.

THE KETOL LXIX (R=H)

Lycoclavinone (LXIX, R=Ac) (0.045 g.) was dissolved in 10% aqueous hydrochloric acid and the solution refluxed for two hours then cooled, basified with sodium bicarbonate and extracted four times with chloroform. Evaporation of the dried chloroform extract and sublimation of the residue gave a colorless solid



(0.023 g.), m.p. 127-132°. Four recrystallizations from Skellysolve B gave the analytically pure ketol, m.p. 135-136°. Occasionally a second crystalline form, m.p. 122-123°, was obtained. The two forms had different infrared spectra in nujol mull, but identical solution spectra (maxima at 3510  $\text{cm}^{-1}$  (bonded hydroxyl) and 1710  $\text{cm}^{-1}$  (ketone) in carbon tetrachloride).

The ultraviolet spectrum showed a maximum at 280  $\text{m}\mu$  ( $\log \epsilon = 1.95$ ), while the ORD curve showed a positive Cotton effect ( $c$  0.11)  $[\phi]_{400} 0 \pm 20^\circ$ ,  $[\phi]_{304} +6,400^\circ$ ,  $[\phi]_{253} -19,100^\circ$ ,  $[\phi]_{250} -19,000^\circ$ .

Found C-72.88, 73.00%: H-9.62, 9.76%: N-5.26%

$\text{C}_{16}\text{H}_{25}\text{O}_2\text{N}$  requires C-72.96%: H-9.57%: N-5.32%

#### ACETYLATION OF THE KETONE LXIX (R=H)

The ketol LXIX, R=H, (0.016 g.) was kept at room temperature for twenty-four hours in a mixture of acetic anhydride (4 ml.) and pyridine (2 ml.). Most of the solvent was removed at the pump at room temperature, leaving a yellow oil which was dissolved in a small volume of ether and eluted rapidly (under pressure) through a short (1 g.) column of alumina with ether eluent.

Evaporation of the ether and crystallization of the residue from n-hexane yielded "lycoclavinone", LXIX, R=Ac, m.p. 173-175° (0.009 g.) whose melting point showed no depression on admixture with an authentic sample of "lycoclavinone".

The liquors from the crystallization were evaporated to dryness, leaving an off-white semisolid (0.005 g.) whose infrared spectrum was virtually identical to that of "lycoclavinone".

#### THE DIOSPHEENOL LXIV

##### (a) From lycoclavinone.

Lycoclavinone (LXIX, R=Ac) (0.053 g.) was stirred at room





temperature for twelve hours in 2% sodium hydroxide in 20% methanol (30 ml.). After this time the ultraviolet spectrum of an aliquot showed a maximum at  $328\text{ m}\mu$  ( $\epsilon=7,600$ ) shifting to  $276\text{ m}\mu$  ( $\epsilon=8,800$ ) on acidification. The solution was then adjusted pH 7.5 with dilute acetic acid and extracted four times with chloroform. Evaporation of the dried chloroform extracts gave a colorless solid which did not readily crystallize and was purified by sublimation, giving a colorless solid (0.042 g.). The analytical sample melted at  $185-186^\circ$ .  $[\alpha]_D - 45$  (0.5 in ethanol).

Found C-73.41%: H-8.95%: O-12.12%: N-5.33%

$\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}$  requires C-73.53%: H-8.87%: O-12.24%: N-5.36%

The infrared spectrum of the diosphenol showed maxima at  $3440\text{ cm}^{-1}$  (bonded OH),  $1672\text{ cm}^{-1}$  (carbonyl) and  $1648\text{ cm}^{-1}$  (carbon-carbon double bond) (in carbon tetrachloride). The nujol spectrum showed the corresponding peaks at 3250, 1668 and  $1643\text{ cm}^{-1}$ .

When the hydrolysis was carried out in an atmosphere of nitrogen the peak at  $327\text{ m}\mu$  developed at about one-seventh the rate in air. When oxygen was bubbled through the reaction solution the rate of formation was about one and a half times that in air.

The ultraviolet spectrum of the pure diosphenol showed a maximum at  $282\text{ m}\mu$ , ( $\log \epsilon=3.99$ ), shifting to  $327\text{ m}\mu$  in ethanolic sodium hydroxide.

Acetylation of the diosphenol LXIV with acetic anhydride-pyridine at room temperature gave an oily product which showed a maximum at  $248\text{ m}\mu$  in the ultraviolet.

(b) From the ketol LXIX.

The ketol LXIX (7.80 mg.) was dissolved in methanol (0.10 ml.) and the volume of the solution made up to 4.00 ml. with 3% aqueous



sodium hydroxide. The solution was stirred at room temperature and the ultraviolet spectra of aliquots measured as indicated below.

TIME	$\lambda_{\max}$ at pH=14	$\epsilon$	$\lambda_{\max}$ at pH=1	$\epsilon$
$\frac{1}{2}$ hour	325 m $\mu$	2,500	280 m $\mu$	2,480
1 hour	327 m $\mu$	3,200	277 m $\mu$	4,350
$4\frac{1}{2}$ hours	327 m $\mu$	6,050	277 m $\mu$	7,850
16 hours	327 m $\mu$	6,500	277 m $\mu$	8,500

(c) From lycopodine.

(i) By basic hydrolysis of the "bromo-complex".

A solution of lycopodine (0.45 g.) in chloroform (20 ml.) was treated with a solution of bromine (0.30 g.) in chloroform (20 ml.). After standing two hours at room temperature the faintly yellow solution was evaporated at the pump. The solid residue was washed with a small volume of cold acetone, leaving a colorless solid (0.57 g.), m.p. 280-295° (dec.). The analytical sample, prepared by three recrystallizations from methanol, melted at 285-295° (dec.).

Found C-51.95, 52.27%: H-6.93, 6.88%: Br-32.09%

$C_{16}H_{26}ONBr \cdot C_{16}H_{25}ONBr_2$  requires C-52.26%: H-6.99%: Br-32.60%

The bromo-complex showed infrared maxima (nujol mull) at 2540  $cm^{-1}$  (+NH) and 1700  $cm^{-1}$  (carbonyl) and an ultraviolet maximum at 303 m $\mu$  ( $\epsilon=120$ ).

By fractional crystallization of the combined mother liquors of several such brominations from methanol-acetone it was possible to isolate small quantities of relatively pure 6 $\alpha$ -bromolycopodine hydrobromide (see below), m.p. 260-269°.





The recrystallized "bromo-complex" (0.30 g.) was stirred overnight with 3% aqueous sodium hydroxide, then the reaction mixture adjusted to pH 7.5 and extracted with ether to give a dark brown oil (0.21 g.). Chromatography of the oil over alumina (5 g.), gave lycopodine (0.091 g.), eluted with ether, and the enolic  $\alpha$ -diketone LXIV (0.036 g.) eluted with chloroform-methanol (99:1).

(ii) By direct oxidation of lycopodine.

A solution of lycopodine LVIII (0.83 g.) in dioxane (70 ml.) was refluxed for eighteen hours with selenium dioxide (0.37 g.). The dark brown solution was then filtered from selenium and the dioxane removed at the pump. The resulting red-brown resin was dissolved in water, the pH adjusted to 7.5 with sodium bicarbonate and the solution extracted six times with chloroform. The reddish-brown oil (0.63 g.) obtained by removal of the chloroform was chromatographed over alumina (12 g.).

Elution with ether gave a pale yellow solid, which proved to be mainly lycopodine (0.30 g.). Elution with chloroform-methanol (49:1) yielded a dark brown semi-solid (0.22 g.) which on sublimation furnished fairly pure diosphenol LXIV, m.p. 183-185°, identical (infrared spectrum, ultraviolet spectrum, m.m.p., optical rotation) to that prepared from lycoclavinone.

Use of excess selenium dioxide in either refluxing dioxane or 90% acetic acid led to the formation of compound(s) absorbing in the ultraviolet at 306, 340 and 380 m $\mu$ . These compounds were not investigated in detail.

These results are illustrated in Table III. In these cases only small scale experiments were undertaken and the course of the



reaction followed from the ultraviolet spectrum.

TABLE III

(a) Using one equivalent of  $\text{SeO}_2$  in refluxing dioxane.

Time (hours)	$\lambda_{\text{max}}$ at pH=1	$\epsilon$	$\lambda_{\text{max}}$ at pH=14	$\epsilon$
$2\frac{1}{2}$	280	1300	325	900
5	276	1650	325	1200
22	276	1700	325	1500

(b) Using two equivalents of  $\text{SeO}_2$  in refluxing dioxane.

Time (hours)	$\lambda_{\text{max}}$ at pH=1	$\epsilon$	$\lambda_{\text{max}}$ at pH=14	$\epsilon$
$1\frac{1}{2}$	280, 306	1450, 600	325, 380	1050, 600
3	280, 310	1550, 750	330, 380	900, 400
23	310	1300	380	1100

(c) Using two equivalents of  $\text{SeO}_2$  in refluxing 90% acetic acid.

Time (hours)	$\lambda_{\text{max}}$ at pH=1	$\epsilon$	$\lambda_{\text{max}}$ at pH=14	$\epsilon$
2	280, 306	1600, 1300	340, 380	1000, 800
6	282, 306	2600, 2800	380	2150
20	282, 306	1800, 1900	383	900

TREATMENT OF DESACETYLLYCOCLAVINE LXVII ( $R=R'=H$ ) WITH PERIODATE

Periodic acid (0.13 g.) was dissolved in water (40 ml.) and three ten ml. portions of this solution used (a) to dissolve desacetyllycoclavine (12.7 mg.) (b) to dissolve trans-1,2-cyclohexanediol (c) as a blank solution.

Each solution was diluted to 50 ml. with 50% ethanol and stirred at room temperature. At the times indicated in the table





below 5 ml. of each solution was removed, neutralized by adding a saturated aqueous solution of sodium bicarbonate (1 ml.) and stirred at room temperature with 10 ml. of 0.04033N sodium arsenite solution. The arsenite remaining was then back-titrated with 0.0485N iodine. The amount of periodate consumed by the diol was calculated in the usual way.

TIME (HOURS)	MOLES PERIODATE CONSUMED	
	TRANS-1,2-CYCLOHEXANEDIOL	DESACETYLLYCOCLAVINE
$\frac{1}{2}$	0.8	0.0
1	1.0	0.0
2		0.0
4		0.0
18		0.1?

# PYROLYSIS OF "LYCOCLAVINONE" LXIX.

Lycoclavinone LXIX (28 mg.) was heated at 240° in a nitrogen atmosphere for eight minutes, then cooled to 120° and vacuum distilled (0.1 mm. Hg). The distillate, a pale yellow oil, was chromatographed over alumina. Elution with ether gave a colorless oil (13 mg.) which showed a maximum in the ultraviolet at 244 mμ (log ε = 3.9) and bands in the infrared at 1680 and 1610 cm<sup>-1</sup>. Treatment of the oil in acetone with methyl iodide yielded a solid methiodide LXXIV.CH<sub>3</sub>I which melted after recrystallization from methanol-ether at 273-274° and showed maxima in the infrared at 1698 and 1629 cm<sup>-1</sup>. The NMR spectrum showed peaks at 3.04τ (single olefinic proton) and 9.18τ (CHCH<sub>3</sub>, doublet, splitting 3.5 c.p.s.).

Found C-52.71, 52.47%: H-6.74, 6.82%



$C_{16}H_{23}ON \cdot CH_3I$  requires C-52.72%: H-6.77%

THE ACETOXY KETONE LXXIII.

A solution of lycoclavine (0.471 g.) and chromium trioxide (0.47 g.) in 98% acetic acid (20 ml.) was kept at room temperature for eighteen hours, then diluted with chloroform (50 ml.) and the resulting solution washed with enough ice-cold dilute ammonium hydroxide to neutralize the acetic acid. The chloroform layer was separated, washed with water and evaporated to give a colorless oil (0.41 g.).

Crystallization from Skellysolve B gave the acetoxy-ketone LXXIII (0.234 g.), m.p. 115-118°.

Found C-71.03, 70.91%: H-8.88, 8.94%: N-4.63%

$C_{18}H_{27}O_3N$  requires C-70.79%: H-8.92%: N-4.59%

The infrared spectrum (nujol mull) showed maxima at 1747 and 1260  $cm^{-1}$  ( $OCOCH_3$ ) and at 1712  $cm^{-1}$  (ketone). The ultraviolet exhibited a peak at 308  $m\mu$  ( $\log \epsilon = 1.85$ ). The NMR showed peaks at 9.03 $\tau$  (doublet,  $J=6.0$  c.p.s., attributed to  $CHCH_3$ ), 7.89 $\tau$  ( $OCOCH_3$ ) and 4.61 $\tau$  (doublet,  $J=9.0$  c.p.s., attributed to the C-5 proton). Finally, the acetoxy ketone had a negative Cotton effect: rotatory dispersion in methanol ( $c$  0.11):  $[\phi]_{589} -200^\circ$ ,  $[\phi]_{500} -500^\circ$ ,  $[\phi]_{333} -5060^\circ$ ,  $[\phi]_{298} +6100^\circ$ ,  $[\phi]_{280} +1100^\circ$ .

THE ACETOXY KETONE LXX.

A solution of lycoclavine (0.390 g.) and chromium trioxide (0.39 g.) in 98% acetic acid (40 ml.) was kept at room temperature for twenty hours, then made basic with cold dilute ammonium hydroxide and extracted four times with chloroform. Evaporation of the dried chloroform extract left a tan-colored oil (0.4 g.), which was dissolved in ether and filtered rapidly through alumina





(5 g.) to give a colorless oil (0.30 g.) which crystallized (0.219 g.) from Skellysolve B. The analytical sample, prepared by two recrystallizations from Skellysolve B followed by sublimation, melted at  $143^{\circ}$ .

Found C-70.96%: H-8.77%: N-4.36%

$C_{18}H_{27}O_3N$  requires C-70.79%: H-8.93%: N-4.59%

The acetoxy-ketone showed maxima in the infrared (nujol mull) at 1732, 1238 (OAc) and  $1720\text{ cm}^{-1}$  (ketone) and in the ultraviolet at  $286\text{ m}\mu$  ( $\log \epsilon = 1.79$ ). The ORD curve in methanol ( $c$  0.1) showed a negative Cotton effect:  $[\phi]_{589} -80^{\circ}$ ,  $[\phi]_{400} -315^{\circ}$ ,  $[\phi]_{312} -2135^{\circ}$ ,  $[\phi]_{280} +190^{\circ}$ ,  $[\phi]_{265} +1000^{\circ}$ . The NMR spectrum showed peaks at  $8.96\tau$  (3H doublet, splitting 5.8 c.p.s., attributed to  $\text{CHCH}_3$ ),  $7.83\tau$  ( $\text{OCOCH}_3$ ), and  $4.73\tau$  (1H doublet,  $J=11.5$  c.p.s., attributed to the C-5 proton).

#### THE EQUILIBRATION LXX TO LXIX.

The acetoxy-ketone LXX ( $R=\text{Ac}$ ) (0.017 g.) was adsorbed on alumina (5 g.) in ether and eluted after three and a half hours. The colorless solid obtained (0.014 g., m.p.  $135-153^{\circ}$ ) was crystallized from n-hexane to give "lycoclavinone" LXIX ( $R=\text{Ac}$ ) (0.009 g.), m.p.  $171-173^{\circ}$ , identical (m.m.p., infrared) to an authentic sample. The infrared spectrum of the residues obtained after evaporation of the mother liquors suggested a mixture of lycoclavinone and LXX ( $R=\text{Ac}$ ).

#### THE ISOMERIZATION OF LXXIII TO LXIX AND LXX.

The acetoxy-ketone LXXIII ( $R=\text{Ac}$ ) (0.050 g.) was adsorbed on alumina (5 g.) in ether and eluted after two hours. Crystallization of the residue from n-hexane gave pure "lycoclavinone" LXIX ( $R=\text{Ac}$ ) (0.032 g.) and crude LXX ( $R=\text{Ac}$ ) (0.016 g.).



ACID HYDROLYSIS OF THE ACETOXY-KETONE LXX (R=Ac).

The acetoxy-ketone (0.049 g.) was refluxed in 10% aqueous hydrochloric acid (25 ml.) for one and a half hours. The cooled solution was neutralized with sodium bicarbonate and continuously extracted with ether to give a colorless oil which, on distillation, furnished a colorless solid (0.035 g.), m.p. 128-133°. The infrared spectrum of this material was identical to that of the ketol LXIX (R=H). Crystallization from n-hexane gave colorless spars, m.p. 134-135°, identical (m.p., m.m.p., infrared) to an authentic sample of the ketol LXIX (R=H).

REDUCTION OF THE KETOL LXIX (R=H)

(a) With lithium aluminum hydride.

The ketol LXIX (R=H) (0.086 g.) was refluxed with a slurry of lithium aluminum hydride (0.15 g.) in ether (50 ml.) for three hours. Working up in the usual manner gave a colorless solid, LXXVII, (0.084 g.), m.p. 217-222°. The analytical sample, m.p. 230-231°, was prepared by crystallization from acetone, followed by sublimation.

Found C-71.78%: H-10.92%: N-5.44%

C<sub>16</sub>H<sub>27</sub>O<sub>2</sub>N requires C-72.41%: H-10.25%: N-5.28%

The infrared spectrum (nujol mull) showed a sharp band at 3500 cm<sup>-1</sup> and broad -OH absorption at 2600-3300 cm<sup>-1</sup>.

(b) With lithium-ammonia-methanol.

A solution of the ketol LXIX (R=H) (0.085 g.) in methanol (10 ml.) was added to liquid ammonia (150 ml.). The solution was stirred vigorously and lithium (0.2 g.) added in small pieces over a period of ten minutes, then the ammonia was evaporated and water (100 ml.) added. Continuous ether extraction yielded a yellow oil,





which, on distillation (0.1 mm., 150°), afforded a colorless oil that solidified on scratching. Four recrystallizations from acetone gave small, colorless needles of diol LXXIX, m.p. 209-210°.

Found (sublimed sample) C-72.38, 72.21%: H-10.52, 10.55%:

N-4.94%

$C_{16}H_{27}O_2N$  requires C-72.41%: H-10.25%: N-5.28%

Analysis of unsublimed material suggested that it was a monohydrate (found C-67.84%: H-9.31%).

The infrared spectrum (nujol mull) showed -OH stretching vibrations at 3580 (sharp) and 3080 (broad)  $cm^{-1}$ . The perchlorate melted at 243-245°. The mixed melting point of the free base with diol LXXVIII (m.p. 207-208°) was 176-184°.

#### THE DIOL LXXVI

The acetoxy-ketone LXX (R=Ac) (0.027 g.) was refluxed with lithium aluminum hydride (0.10 g.) in ether (30 ml.) for six hours, then worked up in the usual manner to give a colorless solid (0.022 g.), m.p. 219-226°. Recrystallization from acetone raised the melting point to 234-235°. The compound, even after sublimation, analyzed as the hemihydrate.

Found C-70.38, 70.04%: H-10.49, 10.32%: N-5.79%

$C_{16}H_{27}O_2 \cdot \frac{1}{2}H_2O$  requires C-70.03%: H-10.28%: N-5.10%

The mixed melting point with diol LXXVII (m.p. 230-231°) was 223-230°.

#### FURTHER BROMINATIONS OF LYCOPODINE.

##### (a) With one-half equivalent of bromine in carbon tetrachloride.

Bromine (0.074 g.) was added to a stirred solution of lycopodine (0.229 g.) in carbon tetrachloride (50 ml.), and the solution, which decolorized immediately, was stirred at room



temperature for thirty minutes. Removal of the solvent from the pale yellow suspension left an almost colorless solid which was washed with acetone (25 ml.), leaving a colorless solid (0.184 g.) whose infrared spectrum (nujol) was identical to that of dihydrolycopodine hydrobromide (XXIX·HBr). Concentration of the acetone solution gave more dihydrolycopodine hydrobromide (0.028 g., total yield 70%).

The remaining acetone solution slowly turned dark brown. Complete removal of the solvent left a dark oil, whose infrared spectrum (chloroform) showed maxima at 1710 (broad), 1670 and 1600  $\text{cm}^{-1}$ . Conversion to the free base in the usual manner gave an intractable dark gum.

(b) With one-half equivalent of bromine in chloroform.

Bromine (0.059 g.) was added to a stirred solution of lycopodine (0.183 g.) in chloroform (35 ml.), and the colorless solution stirred at room temperature for five minutes. Removal of the solvent gave an off-white solid, which, after crystallization from methanol-acetone gave dihydrolycopodine hydrobromide (XXIX·HBr) (0.135 g. - 55%). Evaporation of the mother liquors from the crystallization gave a dark oil whose infrared spectrum was similar to that of the corresponding oil in part (a) above.

(c) With one and two thirds equivalents of bromine in chloroform.

Bromine (0.285 g.) was added to a stirred solution of lycopodine (0.263 g.) in chloroform (50 ml.) and the solution stirred at room temperature for eighteen hours. After this time the solvent was removed from the almost colorless solution, leaving a light orange foam. The crude product was washed with acetone,





leaving an almost colorless solid (0.301 g.) m.p. 230-240° whose infrared spectrum (nujol mull) was almost identical to that of 6 $\alpha$ -bromolycopodine hydrobromide, XC.HBr (see below). Yield 63%.

THE BROMINATION OF LYCOPODINE HYDROBROMIDE.

A solution of bromine (0.78 g.) in chloroform (15 ml.) was added dropwise with stirring to a solution of lycopodine hydrobromide (1.45 g.) in chloroform (30 ml.) to which had been added 0.1 ml. of chloroform saturated with hydrogen bromide. The mixture (a small amount of precipitate formed shortly after the bromine addition was complete) was kept at room temperature overnight, then evaporated at the pump and cold acetone (20 ml.) added to the residual off-white solid. The solid was collected and crystallized once from methanol to give almost pure 6 $\alpha$ -bromolycopodine hydrobromide (XC.HBr, 1.64 g. - 91%, m.p. 261-265° (dec.)).

Two further crystallizations from methanol furnished the analytical sample, m.p. 266-269° (dec.).

Found C-47.25, 47.45%: H-6.32, 6.43%: N-3.44%: Br-39.27%

C<sub>16</sub>H<sub>25</sub>ONBr<sub>2</sub> requires C-47.19%: H-6.19%: N-3.50%: Br-39.25%

The infrared spectrum of XC.HBr showed maxima at 2470 (+NH) and 1711 cm<sup>-1</sup> (ketone) (in chloroform) and at 2550 and 1703 cm<sup>-1</sup> (nujol mull). The ultraviolet spectrum exhibited maximal absorption at 306 m $\mu$  (log  $\epsilon$  = 2.19). The ORD curve showed a positive Cotton effect in methanol ( $c$  0.10):  $[\varphi]_{589} +150^\circ$ ,  $[\varphi]_{400} +910^\circ$ ,  $[\varphi]_{332} +4550^\circ$ ,  $[\varphi]_{280} -6100^\circ$ ,  $[\varphi]_{250} -2300^\circ$ .

SALT EXCHANGE BETWEEN LYCOPODINE AND 6 $\alpha$ -BROMOLYCOPODINE HYDROBROMIDE.

6 $\alpha$ -Bromolycopodine hydrobromide, XC.HBr, (0.154 g.) was stirred with lycopodine (0.094 g.) in chloroform (30 ml.) at room temperature for twenty-four hours. Removal of the solvent at the



pump left a light brown solid, which was washed with ether (40 ml.). The residual off-white solid (0.116 g.) exhibited an infrared spectrum identical to that of lycopodine hydrobromide. Evaporation of the ethereal solution left an orange solid (0.132 g.) whose infrared spectrum was identical to that of 6 $\alpha$ -bromolycopodine XC.

THE REACTION OF BROMINE WITH DIHYDROLYCOPODINE XXIX.

A solution of bromine (0.032 g., one-half equivalent) in chloroform (10 ml.) was added all at once to a stirred solution of dihydrolycopodine (0.098 g.) in chloroform (15 ml.). The mixture, which immediately decolorized, then slowly became yellow, was stirred at room temperature for one hour, then evaporated to dryness, leaving an orange semi-solid. The crude product was washed with cold acetone (5 ml.) and filtered. The residual colorless solid (0.079 g. - 61%) showed an infrared spectrum identical to that of dihydrolycopodine hydrobromide. Concentration of the acetone solution and addition of a little ether led to the precipitation of more XXIX.HBr (0.024 g. - 18%). The mother liquors were evaporated to dryness, leaving a dark, viscous, oil, which showed maxima in the infrared at 3640, 3625, 3400, 1710, 1725, 1640 and 1598  $\text{cm}^{-1}$  (in chloroform). The complex mixture was not investigated in detail.

TREATMENT OF DIHYDROLYCOPODINE HYDROBROMIDE WITH BROMINE.

Bromine (0.056 g., 1.5 equivalents) was added to a stirred solution of dihydrolycopodine hydrobromide (0.076 g.) in chloroform (10 ml.) and stirring continued at room temperature for one hour. Acetone (1 ml.) was added to the yellow solution which was then evaporated to dryness, leaving an almost colorless foam. The latter was washed with a little acetone, leaving pure dihydrolyco-





podine hydrobromide (0.059 g. - 78% of starting weight). The acetone liquors were evaporated to dryness to give a light brown semi-solid, whose infrared spectrum (nujol mull) was very similar to that of dihydrolycopodine hydrobromide, although weak bands at 1725 and 1690  $\text{cm}^{-1}$  indicated that some oxidation had occurred.

THE REACTION OF ACETYLDIHYDROLYCOPODINE XXXIII WITH BROMINE.

A solution of bromine (0.014 g., 0.5 equivalents) in chloroform (10 ml.) was added all at once to a solution of acetyldihydrolycopodine XXXIII (0.055 g.) in chloroform (10 ml.). The solution decolorized immediately and after fifteen minutes was evaporated to dryness to give a light brown foam.

Crystallization from acetone-ether yielded acetyldihydrolycopodine hydrobromide (0.049 g. - 71%) m.p. 259-262° identical (m.p., m.m.p., infrared) to an authentic sample.

The mother liquors from the crystallization yielded a light brown oil on evaporation, which darkened rapidly on standing and failed to yield further crystalline material.

OPTICAL ROTATORY DISPERSION SPECTRA OF LYCOPODINE SALTS.

The salts were prepared by the usual methods:

(a) Lycopodine hydrobromide: RD in methanol ( $c$  0.12):

Negative Cotton effect.

$[\phi]_{589} -330^\circ$ ,  $[\phi]_{500} -430^\circ$ ,  $[\phi]_{400} -600^\circ$ ,  $[\phi]_{305} -2340^\circ$ ,  
 $[\phi]_{268} +430^\circ$ ,  $[\phi]_{253} \pm 0$ .

(b) Lycopodine: RD in acetic acid ( $c$  0.10):

Negative Cotton effect.

$[\phi]_{589} -230^\circ$ ,  $[\phi]_{500} -345^\circ$ ,  $[\phi]_{400} -545^\circ$ ,  $[\phi]_{300} -2270^\circ$ ,  
 $[\phi]_{263} +540^\circ$ ,  $[\phi]_{255} +400^\circ$ .



(c) Lycopodine methiodide: RD in methanol (c 0.12).

Negative Cotton effect.

$[\phi]_{589} -110^\circ$ ,  $[\phi]_{500} -160^\circ$ ,  $[\phi]_{400} -560^\circ$ ,  $[\phi]_{304} -2450^\circ$ ,  
 $[\phi]_{268} +260^\circ$ ,  $[\phi]_{255} \pm 0$ .

(d) Lycopodine perchlorate: RD in methanol (c 0.096).

Negative Cotton effect.

$[\phi]_{589} +80^\circ$ ,  $[\phi]_{500} \pm 0^\circ$ ,  $[\phi]_{400} -360^\circ$ ,  $[\phi]_{302} -1600^\circ$ ,  
 $[\phi]_{260} +280^\circ$ ,  $[\phi]_{250} \pm 0^\circ$ .

6 $\alpha$ -Bromolycopodine XC

A solution of 6 $\alpha$ -bromolycopodine hydrobromide (0.156 g.) in chloroform (60 ml.) was shaken with cold dilute ammonium hydroxide (aqueous sodium bicarbonate gave similar results). The chloroform layer was separated, washed with water, dried over anhydrous magnesium sulphate and evaporated to give a colorless solid (0.12 g.). Crystallization from ether or acetone yielded colorless spars which melted at 163-165° with partial decomposition, then resolidified and melted with decomposition at 238-240°.

Found C-59.63%: H-7.42%: N-4.46%: Br-24.80%

C<sub>16</sub>H<sub>24</sub>ONBr requires C-58.90%: H-7.41%: N-4.29%: Br-24.49%

The bromo compound showed maxima in the infrared at 1702 and 1711 cm<sup>-1</sup> (nujol and carbon tetrachloride respectively) and in the ultraviolet at 305 m $\mu$  (log  $\epsilon$  = 2.22). The NMR showed peaks at 5.82 $\tau$  (CHBr, broadened singlet, half height width 3.2 c.p.s.) and 9.16 $\tau$  (CH-CH<sub>3</sub>, doublet, splitting 3.8 c.p.s.). The rotatory dispersion curve showed a positive Cotton effect: (c 0.064):

$[\phi]_{400} +1070^\circ$ ,  $[\phi]_{335} +8950^\circ$ ,  $[\phi]_{294} -20,550^\circ$ ,  $[\phi]_{250} -4500^\circ$ .

(i.e. Amplitude +29,500). After two and a half hours the amplitude had fallen to +27,250, and after twenty-four hours to





+13,900 . The material recovered from the ORD measurements (24 hours) showed distinct +NH bands in the infrared. When a sample of the 6-bromoketone CI was heated at 170° for one minute the infrared spectrum of the dark solid remaining showed peaks (1690, 1620 and 2520  $\text{cm}^{-1}$ ) characteristic of the unsaturated ketone LXXIV, as well as typical +NH stretching vibrations.

6 $\beta$ -Bromolycopodine hydrobromide (XC.I.HBr)

(a) The 6 $\alpha$ -bromo compound XC.HBr was found to be stable under the following conditions:

i. Chloroform solution with added HBr at room temperature for sixty hours.

ii. Chloroform solution with added 48% HBr/AcOH at room temperature for twenty-four hours.

iii. Chloroform solution with added excess HBr at reflux temperature for twenty-four hours.

(b) Epimerization of the axial bromo compound XC.HBr.

A solution of 6 $\alpha$ -bromolycopodine hydrobromide (XC.HBr) (2.24 g.) in glacial acetic acid (50 ml.) was heated on the steam bath for one hour, then cooled to room temperature and evaporated to dryness under reduced pressure. The residue was washed with cold acetone (50 ml.) and filtered to give a colorless solid (1.71 g.) whose infrared spectrum (nujol) showed maxima at 2450, 1720 and 1703  $\text{cm}^{-1}$ .

Seven recrystallizations from methanol yielded pure 6 $\beta$ -bromolycopodine hydrobromide (XC.I.HBr, 0.21 g.), m.p. 257-262° (dec.).

Found C-47.21, 47.22%; H-6.28, 6.32%; N-3.71; Br-39.62, 39.94%

C<sub>16</sub>H<sub>25</sub>ONBr<sub>2</sub> requires C-47.19%; H-6.19%; N-3.44%; Br-39.25%

The infrared spectrum showed maxima at 2440 and 1728  $\text{cm}^{-1}$  (in



chloroform) attributed to +NH and carbonyl respectively and at 2590, 2550 and 1718  $\text{cm}^{-1}$  (nujol). The ultraviolet spectrum showed a maximum at 276  $\text{m}\mu$  ( $\log \epsilon = 2.07$ ). ORD in methanol ( $c$  0.10):  $[\varphi]_{589} -265^\circ$ ,  $[\varphi]_{500} -400^\circ$ ,  $[\varphi]_{400} -660^\circ$ ,  $[\varphi]_{350} -880^\circ$ ,  $[\varphi]_{310} -1000^\circ$ ,  $[\varphi]_{300} -1290^\circ$ .

Because of the low yields obtained in the epimerization no attempt was made to prepare the free base. When a solution of 6 $\beta$ -bromolycopodine hydrobromide in glacial acetic acid was heated on the steam bath for one hour, the infrared spectrum of the solid recovered after evaporation of the acetic acid was almost identical to that of the starting material.

Reaction of 6 $\alpha$ -bromolycopodine hydrobromide with sodium hydroxide.

6 $\alpha$ -Bromolycopodine hydrobromide (0.35 g.) was suspended in 3% aqueous sodium hydroxide (40 ml.) and stirred at room temperature for eighteen hours. The dark brown solution thus obtained was adjusted to pH 7.5 with acetic acid and extracted four times with chloroform to give a brown semisolid (0.15 g.). The semisolid was chromatographed over alumina (5 g.). Elution with ether yielded the unsaturated ketone LXXIV as a pale yellow oil (0.05 g.). The unsaturated ketone did not readily crystallize and was characterized as the methiodide, m.p. 271-273° after crystallization from acetone, which was found to be identical (m.p., m.m.p., infrared) to that obtained earlier from lycoclavine.

Elution of the chromatogram with chloroform-methanol (49:1) yielded a light brown solid (0.06 g.) which on sublimation afforded the pure diosphenol LXIV (0.041 g.), m.p. 185-186°, identical (m.p., m.m.p., infrared) to that obtained earlier from lycopodine and from lycoclavine.





Lithium-ammonia reduction of the unsaturated ketone LXXIV.

3,4-Dehydrolycopodine (LXXIV, 0.103 g.) in ether (25 ml.) was added to a stirred solution of lithium (0.2 g.) in ammonia (150 ml.). After thirty minutes solid ammonium chloride was added until the blue color disappeared and the ammonia was allowed to evaporate. The residue was distributed between chloroform and water and the layers separated. The aqueous layer was washed with chloroform and the combined organic extracts washed with water. Evaporation of the chloroform left a colorless oil (0.105 g.) which solidified on scratching. The solid material was dissolved in acetone and neutralized with 70% perchloric acid. The perchlorate which separated (0.115 g.) was identical to authentic lycopodine perchlorate.

ALKALOID L.20.

(a) From 6 $\alpha$ -bromolycopodine hydrobromide.

6 $\alpha$ -Bromolycopodine hydrobromide (XC.HBr, 1.32 g.) was added to a stirred solution of 5% aqueous sodium bicarbonate (80 ml.) at room temperature. The bromo compound slowly dissolved but a second crystalline phase began to separate before solution was complete. After twenty-four hours the reaction mixture was transferred to a liquid-liquid extractor and continuously extracted with ether. The ethereal extract was dried over anhydrous magnesium sulphate, filtered, the residues washed well with chloroform and the combined filtrate evaporated to yield an off-white solid (0.78 g., 92%). The infrared spectrum of this material was identical with that of an authentic sample of alkaloid L.20, kindly furnished by Dr. L. Marion, and with a sample of the alkaloid extracted in these laboratories (26) from Lycopodium



lucidulum Michx. The crude product above was crystallized from methanol, giving colorless needles, m.p. 258-259°.

Found C-72.43, 72.57%: H-9.76, 9.81%: N-5.24%

$C_{16}H_{25}O_2N$  requires C-72.96%: H-9.57%: N-5.32%

The infrared spectra showed maxima at 3620 (OH) and 1710  $cm^{-1}$  (ketone) (in chloroform) and at 1713 and 2400-3200  $cm^{-1}$  (nujol).

The ultraviolet spectrum showed a peak at 296  $m\mu$  ( $\log \epsilon = 1.85$ ).

The compound showed a positive Cotton effect: ORD in methanol

( $c$  0.137):  $[\phi]_{500} +105^\circ$ ,  $[\phi]_{400} +400^\circ$ ,  $[\phi]_{330} +4300^\circ$ ,

$[\phi]_{285} -10500^\circ$ ,  $[\phi]_{270} -3000^\circ$ . The natural and synthetic materials were identical in all respects (m.p., m.m.p., infrared, ORD).

(b) From 6 $\beta$ -bromolycopodine hydrobromide XCI.HBr.

6 $\beta$ -Bromolycopodine hydrobromide (XCI.HBr, 0.084 g.) was stirred for twenty-four hours with 5% aqueous sodium bicarbonate (20 ml.) at room temperature. The resulting brown solution was extracted six times with chloroform and the product obtained crystallized from acetone to give alkaloid L.20 (0.019 g., 35%). Although the yield is lower than that quoted in part (a) we believe that this is largely due to the change in reaction conditions (w/v ratio) since the 6 $\alpha$ -bromo compound, XC.HBr, when treated under conditions identical to those described here, gave only a 30% yield of alkaloid L.20.

6 $\beta$ -Hydroxylycopodine from alkaloid L.20.

(a) A solution of alkaloid L.20 (0.045 g.) in n-propanol (10 ml.) containing sodium propoxide (0.080 g.) was shaken in an atmosphere of nitrogen for forty hours, then chloroform (50 ml.) and water (50 ml.) were added. The chloroform layer was separated, washed with water and evaporated. The residue was crystallized





from acetone, yielding 6 $\beta$ -hydroxylycopodine LXIX (R=H) (0.030 g.), m.p. 121-122°, both pure and mixed with an authentic sample. Both samples had identical infrared spectra (in chloroform).

(b) A solution of alkaloid L.20 (0.131 g.) was adsorbed on a column of basic alumina (10 g.) in ether-benzene (1:1). After twelve hours the column was eluted with ether-methanol (1:1) affording a colorless semisolid (0.12 g.) which on sublimation furnished 6 $\beta$ -hydroxylycopodine, LXIX (R=H) (0.103 g.), identical to an authentic sample.

#### THE DEHYDRATION OF ALKALOID L.20.

A solution of alkaloid L.20 (LXXV, R=H, 0.19 g.) in 10% aqueous hydrochloric acid (30 ml.) was heated under reflux for three hours. After cooling, the solution was neutralized with sodium bicarbonate and continuously extracted with ether. The residue (0.18 g.) was triturated with Skellysolve B (in which the starting material is insoluble). The Skellysolve solution was concentrated and the residual oil dissolved in cold acetone (5 ml.) and methyl iodide (1 ml.) added. On standing overnight in the refrigerator crystals (0.23 g.) of 3,4-dehydrolycopodine methiodide (LXXIV.CH<sub>3</sub>I), m.p. 270-273°, separated.

#### THE BASE CATALYZED OXIDATION OF L.20.

Alkaloid L.20 (0.00250 g.) was stirred at room temperature in a 2% solution of sodium hydroxide in methanol-water (1:2) (14.8 ml.). At the times indicated in the table below an aliquot (0.15 ml.) was removed and the ultraviolet spectrum of the solution, after dilution to a volume of 10 ml. with water, was measured both directly and after the addition of one drop of concentrated hydrochloric acid. The ultraviolet data below indicates the



formation of a mixture of the diosphenol LXIV and the unsaturated ketone LXXIV. The pure diosphenol LXIV shows maxima in the ultraviolet at  $276\text{ m}\mu$  ( $\log \epsilon = 3.99$ ) in aqueous acid shifting to  $327\text{ m}\mu$  in aqueous sodium hydroxide. The pure  $\alpha,\beta$  unsaturated ketone shows a single maximum at  $244\text{ m}\mu$  ( $\log \epsilon = 3.9$ ).

Time (minutes)	$\lambda_{\text{max}}$ pH=14	$\epsilon$	$\lambda_{\text{max}}$ pH=1	$\epsilon$
5	240	1800		
50	240, 327	2500, 800		
105	240, 327	2800, 1400	276	1600
250	327	4000	276	5050

#### ACETYLATION OF THE DIOSPHEENOL LXIV.

The enolic  $\alpha$ -diketone LXIV (0.031 g.) was kept for sixteen hours in a mixture of acetic anhydride ( 4 ml. ) and pyridine ( 1 ml. ) at room temperature. The solvents were removed at the pump, the residues dissolved in ether and chromatographed on a column of basic alumina ( 2 g. ). Elution with ether gave an almost colorless oil ( 0.025 g. ). The infrared spectrum of this oil ( in carbon tetrachloride ) indicated virtually pure enol acetate LXIV ( OH replaced by OAc )





with maxima at 1756 , 1686 , 1200 and 1186  $\text{cm}^{-1}$  ( enol acetate ) and at 1721  $\text{cm}^{-1}$  ( ketone ). The peaks characteristic of the diosphenol were now absent. The ultraviolet spectrum of the crude product showed maximal absorption at 248  $\text{m}\mu$ . The unstable product was not investigated in detail.

#### ACETYLATION OF ALKALOID L.20.

##### (a) At room temperature, formation of enol acetate XCIII.

A solution of alkaloid L.20 (LXXV,  $\text{R}=\text{H}$ , 0.31 g.) in acetic anhydride-pyridine (9 ml. of 1:1) was kept at room temperature for twelve hours, then diluted with chloroform and ice-cold dilute ammonium hydroxide. The chloroform layer was separated and the aqueous layer extracted twice more with chloroform. The combined organic extract was washed with water, dried over anhydrous magnesium sulphate and evaporated to give a colorless oil (0.39 g.). The oil could not be induced to crystallize and was purified and characterized as the perchlorate, formed in acetone and recrystallized from acetone-ether, which melted at 258-259° (dec.).

Found C-53.78%: H-6.82%: N-3.03%

$\text{C}_{20}\text{H}_{29}\text{O}_4\text{N}.\text{HClO}_4$  requires C-53.63%: H-6.75%: N-3.11%

The infrared spectrum of the perchlorate (nujol) showed maxima at 3060  $\text{cm}^{-1}$  (+NH), 1740  $\text{cm}^{-1}$  (two OAc) and 1680  $\text{cm}^{-1}$  (C=C). The free base (in carbon tetrachloride) exhibited maxima at 1760 and 1735  $\text{cm}^{-1}$  (two OAc) and at 1680 (C=C). The NMR spectrum of the free base showed signals at 5.02 $\tau$  (1H, broadened singlet, half



height width 4 c.p.s.), 7.98 and 8.06 $\tau$  (total of 6H) and 9.17 $\tau$  (3H, doublet, splitting 5.5 c.p.s.).

(b) At -10°, formation of acetyl-L.20.

A solution of alkaloid L.20 (0.12 g.) in acetic anhydride-pyridine (7 ml. of 5:2) was kept at -10° for four hours, then poured into chloroform and dilute aqueous ammonia. The aqueous layer was separated and washed twice more with chloroform. The combined chloroform extracts, after washing with water and drying over anhydrous magnesium sulphate, were evaporated to give a colorless solid (0.11 g.), m.p. 126-134°. Three recrystallizations from n-hexane gave analytically pure needles of acetyl-L.20 (LXXV, R=Ac, 0.058 g.), m.p. 143-144°.

Found C-70.97, 70.66%: H-8.92, 8.82%: N-4.72%

C<sub>18</sub>H<sub>27</sub>O<sub>3</sub>N requires C-70.79%: H-8.92%: N-4.59%

The keto acetate showed maxima in the infrared at 1755 (OAc), 1723 (ketone) and 1230 cm<sup>-1</sup> (OAc) (in carbon tetrachloride) and in the ultraviolet at 300 m $\mu$  (log  $\epsilon$ =1.95). The NMR spectrum showed signals at 5.11 $\tau$  (CHOAc, doublet, splitting 3.5 c.p.s.), 7.94 $\tau$  (OCOCH<sub>3</sub>) and 9.16 $\tau$  (CHCH<sub>3</sub>, doublet, J=4.5 c.p.s.). The optical rotatory dispersion spectrum showed a positive Cotton effect with extrema at 327 m $\mu$  (+1800°) and 282 m $\mu$  (-10900°). The perchlorate of the keto acetate, after crystallization from acetone-ether, melted at 229-230° (dec.).

#### LYCOPODINE ENOL ACETATE XCV.

The method used was that of Barton et al (93). A solution of lycopodine (0.5 g.) and p-toluenesulphonic acid (0.45 g.) in acetic anhydride (25 ml.) was heated until the acetic anhydride slowly distilled. After four hours most of the acetic anhydride





had been removed. The residue was diluted with ether, dilute aqueous sodium hydroxide added and the mixture shaken. The aqueous layer was washed twice more with ether. The combined ethereal extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated, leaving an off-white solid which was crystallized from acetone to give lycopodine enol acetate, XCV, (0.44 g.), m.p. 98-100°. The analytical sample was prepared by recrystallization from acetone, then from Skellysolve B and melted at 100-101°.

Found C-74.30, 74.49%: H-9.24, 9.40%: O-11.49%

C<sub>18</sub>H<sub>27</sub>O<sub>2</sub>N requires C-74.70%: H-9.41%: O-11.06%

The infrared spectrum of XCV (in carbon tetrachloride) showed maxima at 1755 cm<sup>-1</sup> (OAc) and 1696 cm<sup>-1</sup> (C=C), and the NMR at 7.86τ (3H, OCOCH<sub>3</sub>) and 9.12τ (3H, CHCH<sub>3</sub>, doublet, J= 6 c.p.s.).

#### THE HYDROLYSIS OF THE ENOL ACETATE XCIII.

##### (a) Acid hydrolysis at reflux temperature.

A solution of the enol acetate perchlorate, XCIII.HClO<sub>4</sub>, (0.061 g.) in 10% aqueous hydrochloric acid (25 ml.) was refluxed for two hours. The solution was cooled, neutralized with sodium bicarbonate and continuously extracted with ether, giving a light tan solid. Crystallization from acetone gave L.20 (0.022 g. - 62%) identical (m.p., m.m.p., infrared) with an authentic sample. The mother liquors from the crystallization were evaporated to dryness and the residual brown semisolid distilled to give almost pure 3,4-dehydrolycopodine LXXIV (0.012 g.).

##### (b) Acid hydrolysis at room temperature.

A solution of the enol acetate XCIII (0.390 g.) in 8% aqueous hydrochloric acid (20 ml.) was stirred at room temperature for





three hours. The solution was neutralized with sodium bicarbonate and extracted four times with chloroform, yielding an almost colorless oil (0.365 g.), which soon turned yellow. The crude product was eluted quickly through a short (5 g.) column of basic alumina with methylene dichloride as eluent, giving a colorless oil (0.269 g.). Crystallization from n-hexane gave O-acetyl L.20 (LXXV, R=Ac, 0.120 g.) m.p. 143-144°, identical to an authentic sample. The infrared spectrum of the oil remaining after evaporation of the mother liquors was almost identical to that of the enol acetate XCIII.

Continuation of the chromatogram above with methanol eluent (again rapid elution in case of epimerization) gave a deep yellow oil (0.065 g.), whose infrared spectrum suggested a mixture of L.20 and O-acetyl L.20.

(c) Base catalyzed hydrolysis at room temperature.

A solution of the enol acetate XCIII (0.087 g.) and sodium bicarbonate (0.5 g.) in 10% aqueous methanol (20 ml.) was stirred at room temperature for twelve hours. Extraction with chloroform (four times) gave a very pale yellow solid which, after crystallization from acetone, gave L.20 (0.024 g. - 38%). The mother liquors from the crystallization were evaporated to dryness and the residues distilled to give a colorless oil (0.014 g.) whose infrared spectrum indicated a mixture of the enol acetate XCIII, a keto acetate and a small amount of the unsaturated ketone LXXIV.

THE HYDROLYSIS OF O-ACETYL L.20 (LXXV, R=Ac).

The keto acetate perchlorate LXXV.HClO<sub>4</sub> (R=Ac) (0.021 g.), was refluxed for one hour in 10% aqueous hydrochloric acid (20 ml.). The solution was cooled, neutralized with sodium bicarbonate, and





continuously extracted with ether, giving an almost colorless solid (0.014 g.). Crystallization from acetone furnished pure L. 20 (0.005 g.), identical (m.p., m.m.p., infrared) with an authentic sample.

The mother liquors from the crystallization were evaporated to dryness to give an almost colorless oil, whose infrared spectrum indicated a mixture of the unsaturated ketone LXXIV, L.20 and a keto acetate.

ATTEMPTED EPIMERIZATION OF O-ACETYL L.20 ON ALUMINA.

The acetoxy-ketone LXXV ( $R=Ac$ ) (0.050 g.) was adsorbed on a column of alumina (10 g.) and eluted with ether after sixteen hours. The infrared spectrum of the pale yellow oil (0.031 g.) eluted with ether, indicated a mixture of the unsaturated ketone LXXIV, a keto acetate and a ketol. The ketol was presumably  $6\beta$ -hydroxylycopodine, since L.20 is known to epimerize on alumina. The keto acetate appeared to be  $6\beta$ -acetoxylycopodine, since the infrared band at  $1240\text{ cm}^{-1}$  is characteristic of that compound. No attempt was made, however, to separate the complex mixture.

THE ACETOLYSIS OF  $6\alpha$ -BROMOLYCOPODINE HYDROBROMIDE, XC.HBr.

A solution of  $6\alpha$ -bromolycopodine hydrobromide XC.HBr, (0.750 g.) and sodium acetate (1.60 g.) in acetic acid-acetic anhydride (55 ml., 3:1 ratio) was refluxed for seven hours. The solution was cooled, ice added, and the solution neutralized with aqueous ammonia. Extraction with ether gave a yellow oil (0.62 g.) which was chromatographed over alumina (20 g.). Elution with ether gave an almost colorless oil (0.461 g.), whose infrared spectrum was almost identical to that of the enol acetate XCIII. Conversion to the perchlorate in acetone, followed by crystallization from



acetone-ether gave the pure enol acetate perchlorate XCIII.HClO<sub>4</sub> (0.337 g., 41%), m.p. 258-259°, identical (m.p., m.m.p., infrared) to an authentic sample. The mother liquors were evaporated to dryness and the residue converted to the free base in the usual way. The oily mixture appeared to be (infrared) a mixture of the unsaturated ketone LXXIV and keto acetate(s). This mixture proved to be very difficult to separate. Hydrolysis (refluxed four hours with 10% aqueous hydrochloric acid) gave mainly the unsaturated ketone LXXIV (10% overall yield from the bromo compound) which was purified as the methiodide.

In another experiment a small (5%) yield of 6 $\alpha$ -acetoxylycopodine LXXV (R=Ac) was obtained by direct crystallization of the crude product, in addition to the good yield of the enol acetate XCIII purified as the perchlorate.

The acetolysis led to extensive decomposition, however, and in all cases the total purified products amounted to less than 50% overall.

THE ACETOLYSIS OF 6 $\beta$ -BROMOLYCOPODINE HYDROBROMIDE XCI.HBr.

A solution of 6 $\beta$ -bromolycopodine hydrobromide (0.270 g.) and sodium acetate (0.41 g.) in a mixture of acetic acid (19.5 ml.) and acetic anhydride (0.5 ml.) was refluxed for eight hours in an atmosphere of nitrogen. Ice was then added and, after neutralization with aqueous ammonia, the solution extracted four times with chloroform, giving a light tan oil (0.19 g.). Chromatography over basic alumina (3 g.) gave, with n-hexane eluent, the unsaturated ketone LXXIV (0.10 g., 62%) and, with ether eluent, 6 $\alpha$ -acetoxylycopodine (0.052 g., 25%) each being identified after purification in the usual way and comparison with an authentic





sample.

REACTION OF THE ETHER LIV WITH BORON TRIFLUORIDE-ACETIC ANHYDRIDE.

A solution of the ether LIV (0.079 g.) in acetic anhydride (2 ml.) and boron trifluoride etherate (0.5 ml.) was kept at room temperature for eighteen hours. Most of the solvents were removed at the pump and the residues dissolved in chloroform. The solution was shaken with dilute aqueous ammonia for one minute the layers separated and the aqueous solution extracted twice more with chloroform. The combined organic extracts were shaken three times with dilute aqueous hydrochloric acid, the aqueous solution extracted once with chloroform, basified with aqueous ammonia and extracted four times with chloroform, giving a colorless oil (0.13 g.), which, on distillation (160°, 1 mm.) furnished a colorless solid (0.079 g.). Crystallization from ether containing a little n-hexane furnished the pure pyridine CII (0.061 g.), m.p. 167-167.5°.

Found C-                      %: H-                      %: N-                      %

C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>N<sub>2</sub> requires C-71.71%: H-7.66%: N-7.63%.

The amido-acetoxy-pyridine showed maxima in the infrared at 1728, 1639, 1627, 1590, 1510 and 1240 cm<sup>-1</sup> (nujol) and at 1732, 1636, 1585 and 1225 cm<sup>-1</sup> (carbon tetrachloride). The ultraviolet spectrum showed peaks at 269 mμ (log ε=3.63) and 276 mμ (log ε=3.60) (in ethanol) and at 273 mμ (log ε=3.91) (in ethanol/H<sup>+</sup>). The NMR showed signals at 3.18τ (one aromatic proton), 7.55τ (6H - two aromatic methyl groups) and 8.70τ (3H, OCOCH<sub>3</sub>). The molecular weight was 368 (from mass spectrum).

REDUCTION OF THE AMIDO-PYRIDINE CII.

The amido-pyridine (0.049 g.) was refluxed with lithium



aluminum hydride (0.15 g.) in dry ether (50 ml.) for twenty hours. The reaction mixture was worked up in the usual way to give a colorless oil (0.038 g.) which solidified on scratching, m.p. 216-229°. Crystallization from acetone followed by sublimation furnished the analytical sample m.p. 232-234°.

Found C-77.12, 77.57%: H-8.89, 9.06%: N-8.44%

C<sub>20</sub>H<sub>28</sub>ON<sub>2</sub> requires C-76.88%: H-9.03%: N-8.96%

The mass spectrum indicated a molecular weight of 312. The hydroxy pyridine CIV showed maxima in the infrared at 3300, 1592 and 1562 (nujol) and at 3600 cm<sup>-1</sup> with no absorption between 1600 and 2900 cm<sup>-1</sup> (in carbon tetrachloride). The NMR showed a one-proton singlet at 3.33 $\tau$  (aromatic proton) and a six proton singlet at 7.61 $\tau$  (two aromatic methyl groups). The ultraviolet spectrum showed maxima at 268 m $\mu$  (log  $\epsilon$  = 3.19) and 276 m $\mu$  (log  $\epsilon$  = 3.17) in ethanol, shifting to a single peak at 275 m $\mu$  (log  $\epsilon$  = 3.48) after the addition of one drop of concentrated hydrochloric acid.

#### ACETYLATION OF THE HYDROXY PYRIDINE CIV.

The hydroxy pyridine (0.017 g.) was heated on the steam bath for sixteen hours in acetic anhydride (2 ml.) and pyridine (1 ml.). Most of the solvent was removed at the pump, the residue dissolved in dilute hydrochloric acid and the aqueous solution extracted twice with ether. The acidic solution was basified with aqueous ammonia and extracted four times with chloroform to give a light brown oil (0.02 g.) which on distillation furnished a pale yellow solid (0.018 g.). The infrared spectrum (nujol) of the basic product showed strong maxima at 1730, 1235 and 1223 cm<sup>-1</sup> (O-acetate) and at 1590 and 1562 cm<sup>-1</sup> (pyridine ring) and very little hydroxyl absorption, indicating that acetylation was virtually complete.





The NMR spectrum showed signals at 3.20 $\tau$  (1H, singlet, aromatic proton), 5.16 $\tau$  ( $\text{CHOAc}$ ), 7.58 $\tau$  and 7.60 $\tau$  (total of 6H, two aromatic methyl groups) and 8.78 $\tau$  (3H, singlet,  $\text{OCOCH}_3$ ).

CLEAVAGE OF THE 5:15 ETHER LIV WITHOUT PYRIDINE FORMATION.

(a) The ether LIV was recovered unchanged after treatment under the following conditions:

(i) A solution of the ether (0.033 g.) in 95% acetic acid (2.2 ml.) with added 48% hydrobromic acid in glacial acetic acid (0.2 ml.) was heated on the steam bath for ten hours.

(ii) The ether (0.029 g.) was stirred at room temperature for twelve hours in glacial acetic acid (2 ml.) with added boron trifluoride etherate (0.5 ml.)

(iii) The ether (0.056 g.) was heated on the steam bath for one hour in a mixture of acetic acid (0.1 ml.) and acetic anhydride (2 ml.).

(iv) The ether (0.028 g.) was heated on the steam bath for one and a half hours in glacial acetic acid (10 ml.) with chromium trioxide (0.035 g.).

(b) Reaction with boron trifluoride-acetic anhydride in ether.

Boron trifluoride etherate (2 ml.) was added to a stirred solution of the epoxylactam LIV (0.093 g.) in a mixture of acetic anhydride (2 ml.) and ether (15 ml.) and the solution kept at room temperature for forty-eight hours. More ether (30 ml.) was added and the mixture shaken for five minutes with aqueous ammonia. The layers were separated and the aqueous layer shaken twice with chloroform. The combined organic extracts were evaporated to small volume, more chloroform added and shaken with dilute hydrochloric acid. The latter was basified with aqueous ammonia and





extracted four times with chloroform, yielding only a trace of basic reaction products. The original chloroform solution was evaporated to give neutral products as a deep yellow oil (0.11 g.) which, after chromatography over alumina (3 g.) with chloroform eluent, gave an almost colorless oil (0.087 g.). The colorless oil showed maxima in the infrared at 1730 and 1227  $\text{cm}^{-1}$  (acetate) and 1630 and 1635  $\text{cm}^{-1}$  (lactam) in carbon tetrachloride, with no hydroxyl absorption and no peaks attributable to pyridine derivatives. The NMR spectrum showed signals at 8.30 $\tau$  (3H, singlet, attributed to  $-\overset{|}{\underset{|}{\text{C}}}=\text{C}-\text{CH}_3$ ), 8.06 $\tau$  (3H, singlet,  $\text{OCOCH}_3$ ) and peaks in the olefinic proton region at 4.56 $\tau$  (doublet, splitting 6.5 c.p.s.) and 4.70 $\tau$  (low intensity singlet) totalling approximately one proton. No attempt was made to purify the crude unsaturated acetate.

#### REDUCTION OF THE UNSATURATED ACETATE.

The crude acetate (0.068 g.) was refluxed in dry ether (40 ml.) with lithium aluminum hydride (0.15 g.) for four hours. Work up in the usual manner yielded an almost colorless oil (0.06 g.) which, after chromatography over alumina (7 g.) with ether eluent, yielded a colorless oil (0.037 g.). The mass spectrum showed a molecular weight of 247, the infrared spectrum (in carbon tetrachloride) showed a maximum at 3550  $\text{cm}^{-1}$  and no carbonyl absorption. Conversion to the perchlorate in acetone-ether yielded a semicrystalline product (19 mg.) which showed a maximum in the infrared at 3490  $\text{cm}^{-1}$  and a very weak band at 1620  $\text{cm}^{-1}$ . Conversion to the free base gave a colorless oil which showed signals in the NMR at 4.28 $\tau$  (1H, doublet  $J=5.0$  c.p.s., attributed to the C-8 olefinic proton) and 8.33 $\tau$  (3H, doublet





with very small splitting, attributed to  $\text{CH}=\text{CCH}_3$ ).

PYRIDINE FORMATION FROM THE UNSATURATED ACETATE.

Boron trifluoride etherate (0.5 ml.) was added to a stirred solution of the crude unsaturated acetate (12 mg.) in acetic anhydride (2 ml.) and the mixture kept at room temperature for twelve hours. Most of the solvents were removed at the pump, the residues dissolved in chloroform and shaken for one minute with aqueous ammonia. The basic solution was extracted once more with chloroform and the combined organic extracts shaken twice with dilute hydrochloric acid. The acidic solution was basified with aqueous ammonia and extracted twice with chloroform to give a yellow foam which on distillation yielded a pale yellow solid (9.5 mg.), m.p.  $147-156^\circ$ . The infrared spectrum of this material was identical to that of the amido acetoxypyridine CII described above.

1:3-DIMETHYL-5:6:7:8-TETRAHYDROISOQUINOLINE CVII.

Boron trifluoride etherate (8 ml.) was added to a solution of 1-methylcyclohexene (1.128 g.) in acetic anhydride (15 ml.) and the solution kept at room temperature for twelve hours. Most of the solvents were removed at the pump and the residues dissolved in chloroform (50 ml.) which was shaken for five minutes with aqueous ammonia. The chloroform layer was removed and extracted twice with dilute hydrochloric acid. The combined acid extract was shaken twice with chloroform, basified with aqueous ammonia and extracted twice with chloroform. The chloroform solution of the basic products was dried over magnesium sulphate and the solvent removed, leaving a deep yellow oil (0.47 g.), which after distillation at  $84^\circ/0.1$  mm. furnished a colorless oil (0.45 g.).



The mass spectrum of the oil showed a molecular weight of 161. The infrared spectrum (film) showed maxima at 1590 and 1560  $\text{cm}^{-1}$  while the ultraviolet region showed absorption at 268  $\text{m}\mu$  ( $\log \epsilon = 3.48$ ) and 271  $\text{m}\mu$  ( $\log \epsilon = 3.47$ ) shifting to 273  $\text{m}\mu$  ( $\log \epsilon = 3.78$ ) after addition of one drop of concentrated hydrochloric acid. The NMR showed peaks at 3.28 $\tau$  (one aromatic proton) and 7.57 $\tau$  (6H, two aromatic methyl groups).

The picrate, after crystallization from ethanol, melted at 105-106 $^{\circ}$  and the chloroplatinate at 221-222 $^{\circ}$ .

#### THE BASIC ETHER CVIII.

The 5:15 epoxy  $\alpha$ -lactam LIV (0.041 g.) was refluxed for twelve hours in anhydrous ether (50 ml.) with lithium aluminum hydride (0.15 g.). The reaction mixture was worked up in the usual way to give a colorless oil (0.031 g.). This was freed of non-basic material by acid/base extraction with ether to give a colorless oil (0.022 g.) which, after distillation, could not readily be crystallized either as the free base or perchlorate. The free base showed no absorption in the carbonyl or hydroxyl regions in the infrared. The mass spectrum showed the molecular weight to be 247.

#### REACTION OF THE ETHER CVIII WITH BORON TRIFLUORIDE-ACETIC ANHYDRIDE.

Boron trifluoride etherate (0.3 ml.) was added to a stirred solution of the ether CVIII (11 mg.) in acetic anhydride (1 ml.) and the solution kept at room temperature for one and a half hours. Most of the solvent was removed at the pump and the residue dissolved in chloroform (30 ml.) and the solution was shaken with aqueous ammonia for two minutes. The chloroform layer was shaken twice with dilute hydrochloric acid, the latter





extracted once with chloroform, basified with aqueous ammonia and extracted twice with chloroform to give the basic reaction products which, after distillation, yielded a pale yellow oil (4 mg.). The infrared spectrum indicated that ether cleavage had again yielded an acetoxy pyridine, since the product showed maxima at 1738 and 1220  $\text{cm}^{-1}$  (acetoxy) and absorption in the 1500-1600  $\text{cm}^{-1}$  region (in carbon tetrachloride). The ultraviolet spectrum showed peaks at 268  $\text{m}\mu$  and 276  $\text{m}\mu$  shifting to a single peak at 273  $\text{m}\mu$  on acidification. The scale of the experiment prevented a detailed examination of the product.



ULTRAVIOLET SPECTRA





FIGURE 1

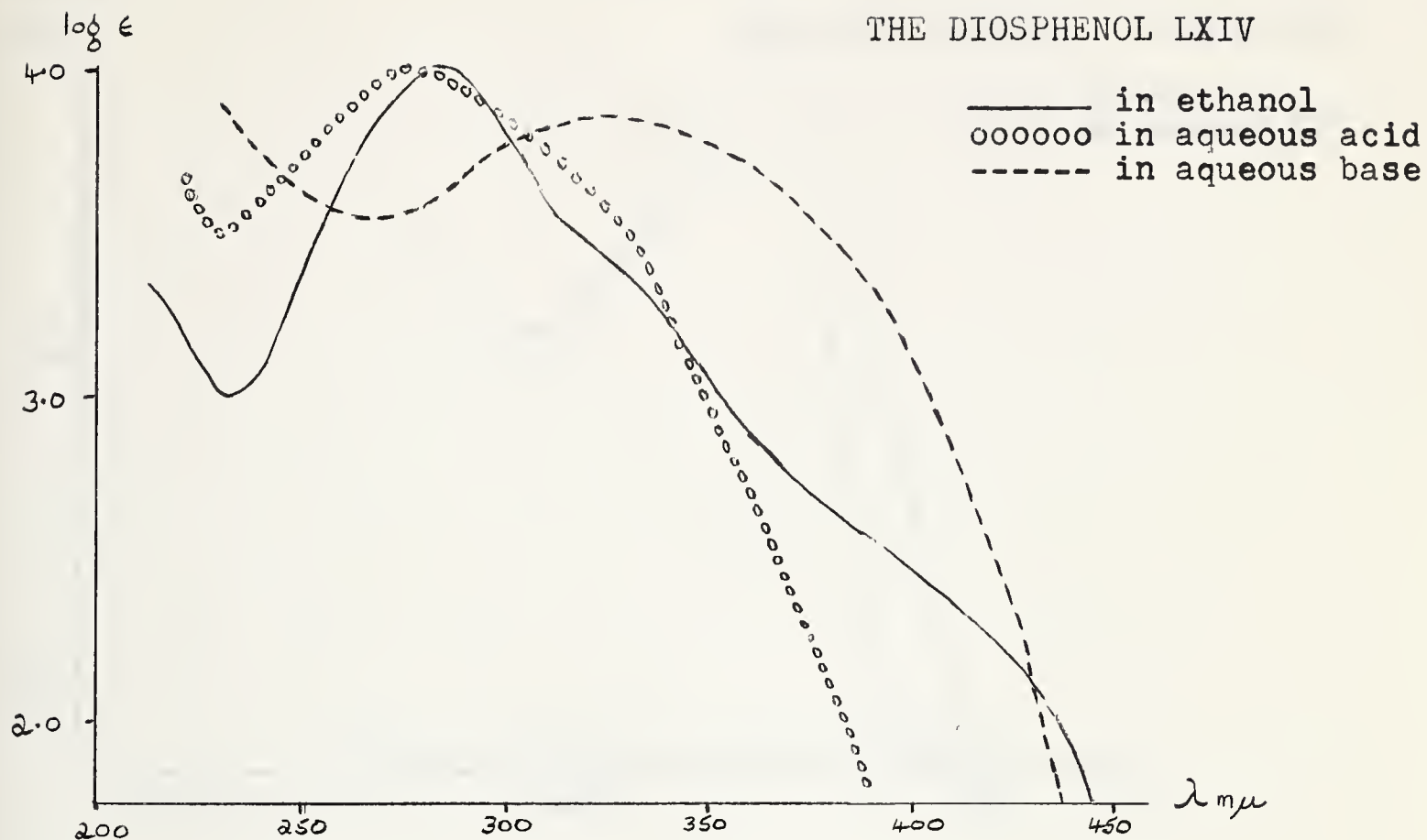


FIGURE 2

3:4 DEHYDROLYCOPODINE LXXIV

in ethanol

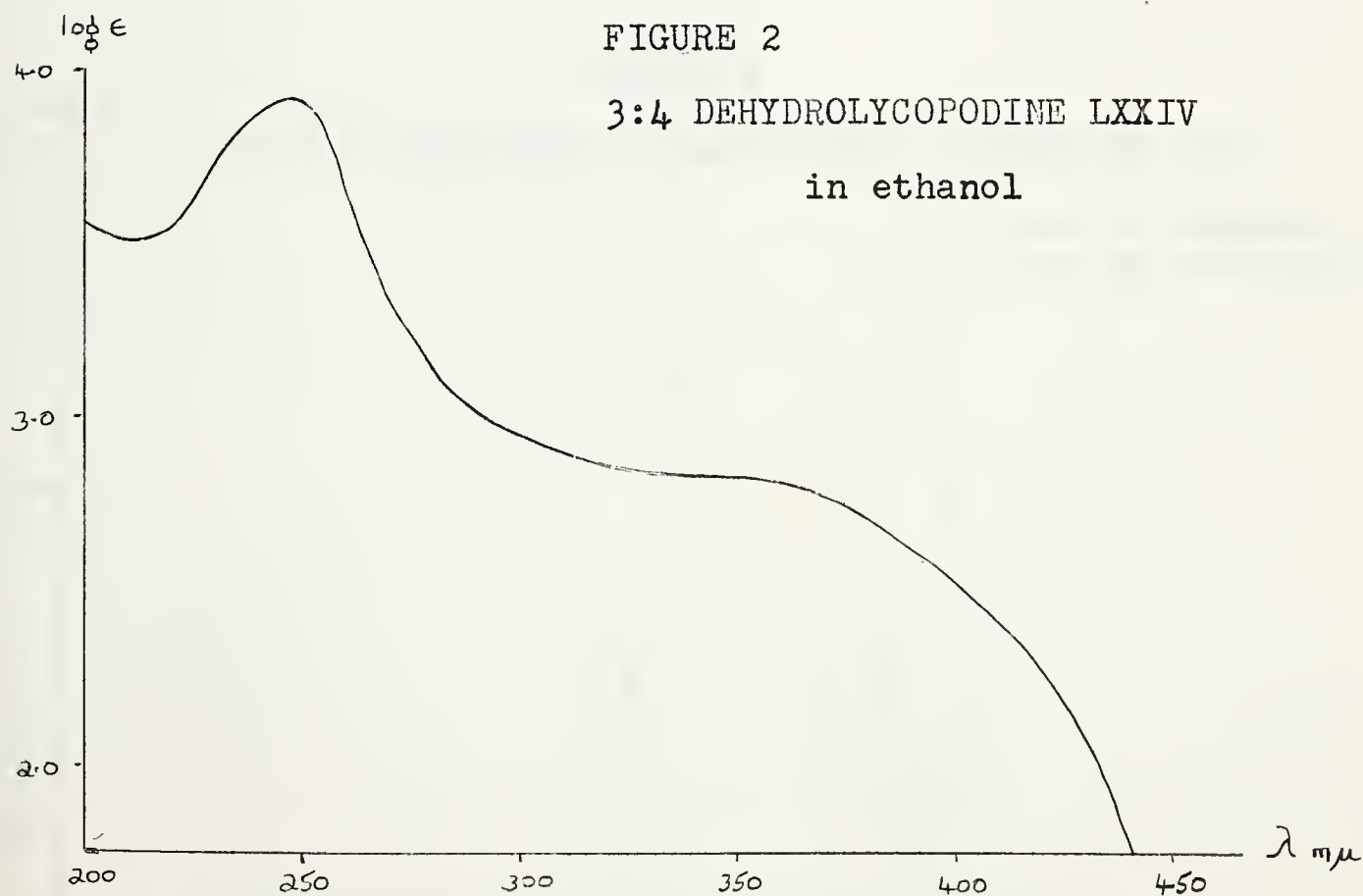




FIGURE 3

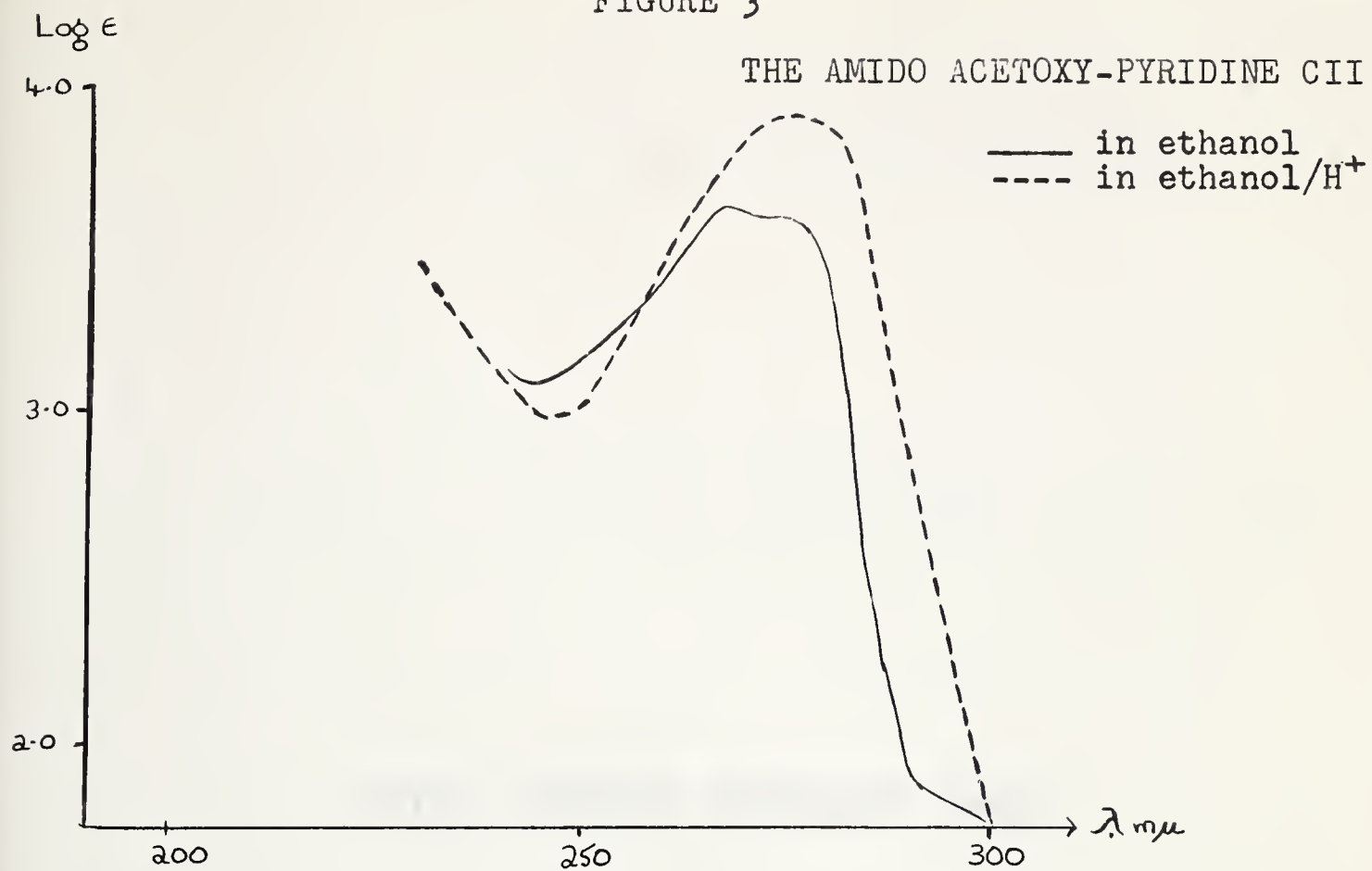
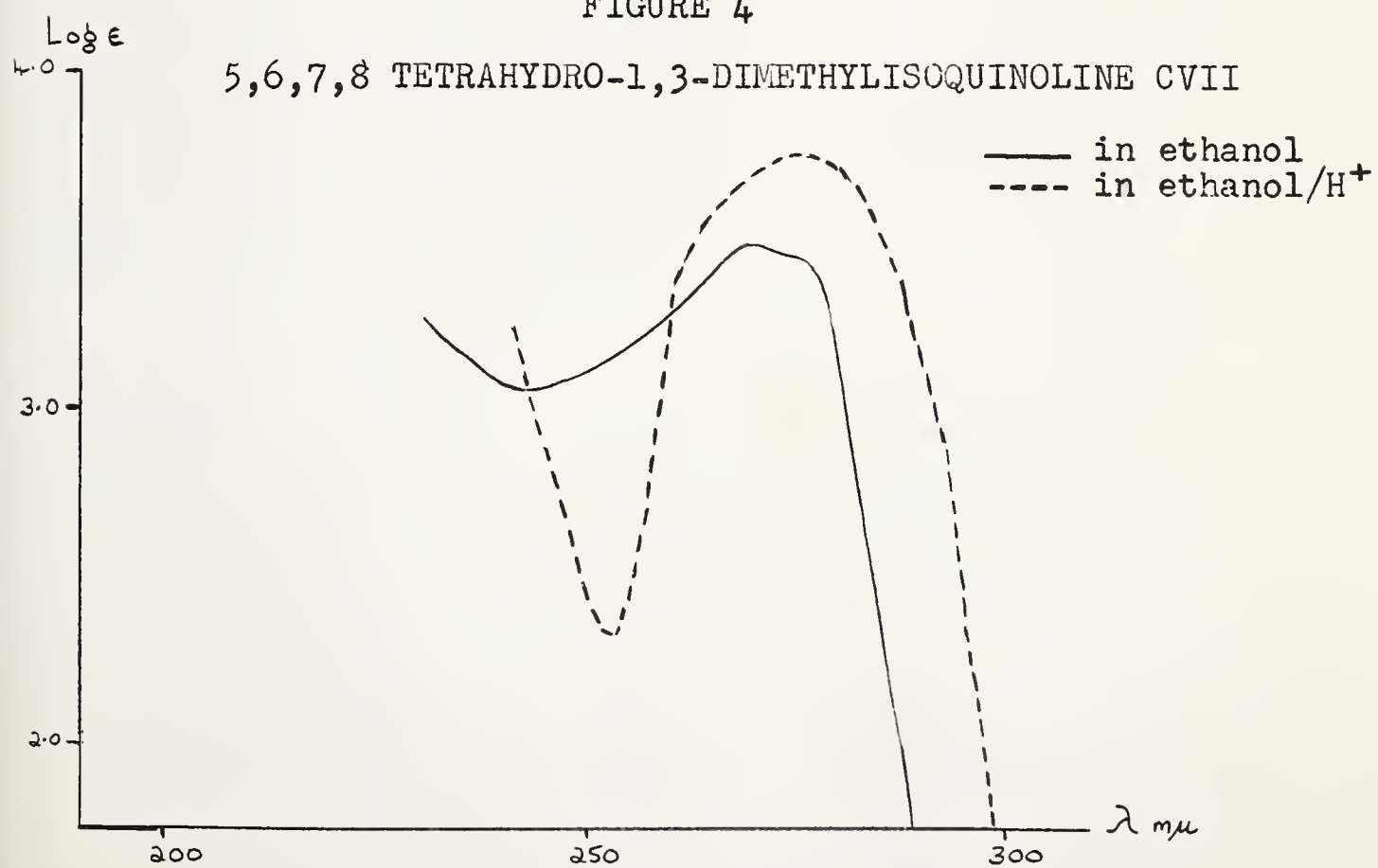


FIGURE 4

5,6,7,8 TETRAHYDRO-1,3-DIMETHYLISOQUINOLINE CVII







OPTICAL ROTATORY DISPERSION CURVES



FIGURE 5

OPTICAL ROTATORY DISPERSION CURVE OF  
LYCOPODINE IN METHANOL

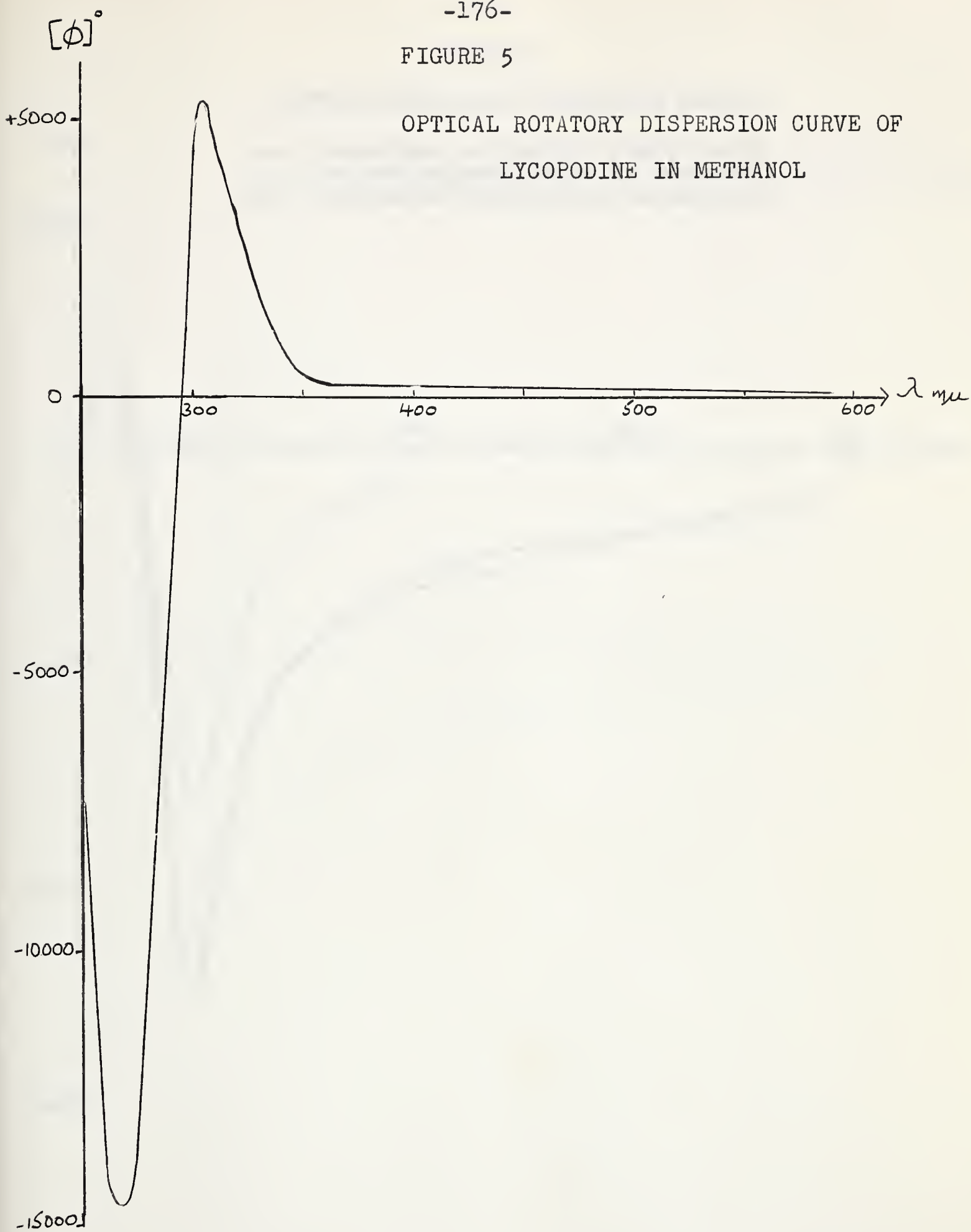






FIGURE 6

OPTICAL ROTATORY DISPERSION CURVES

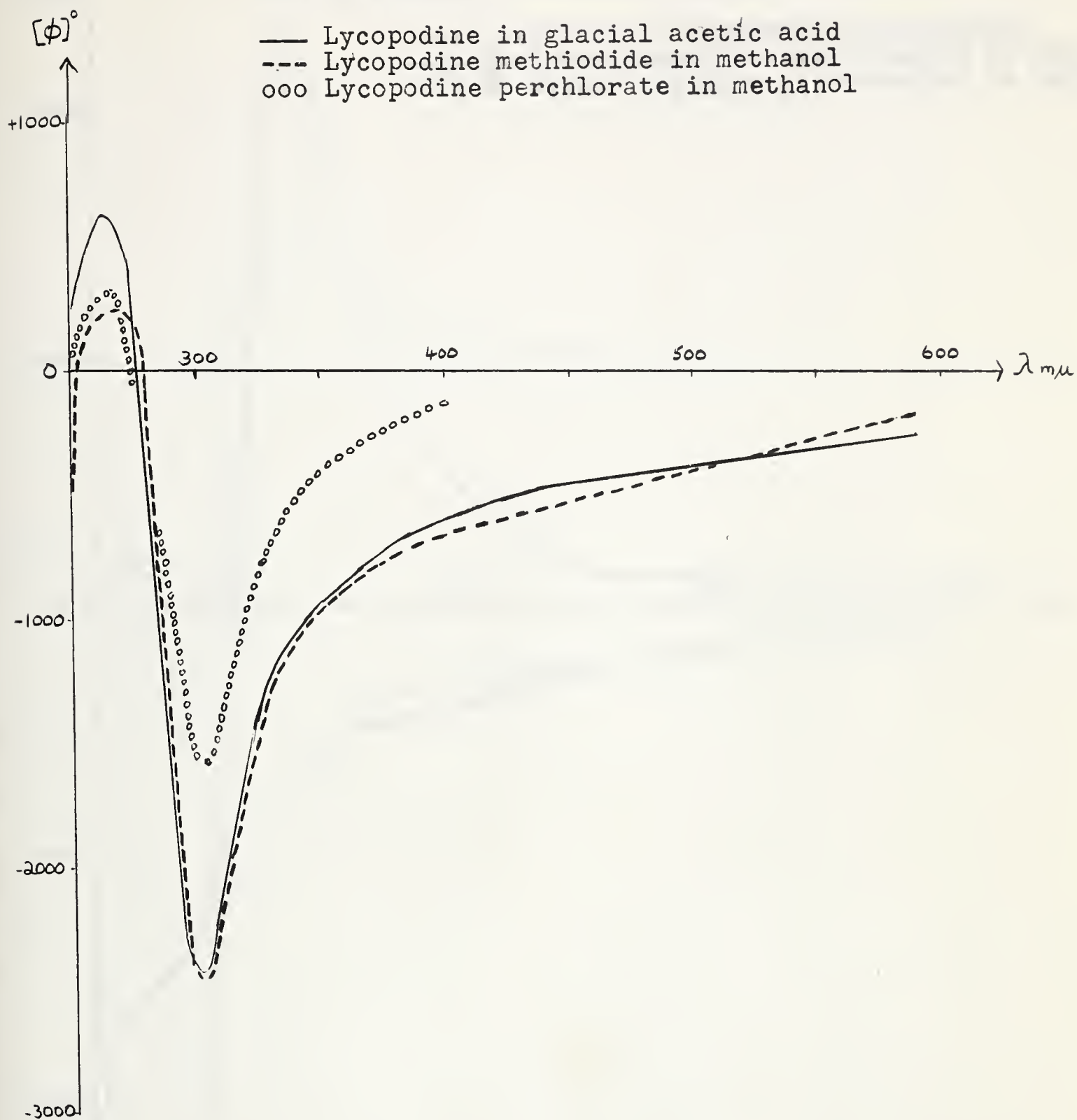




FIGURE 7

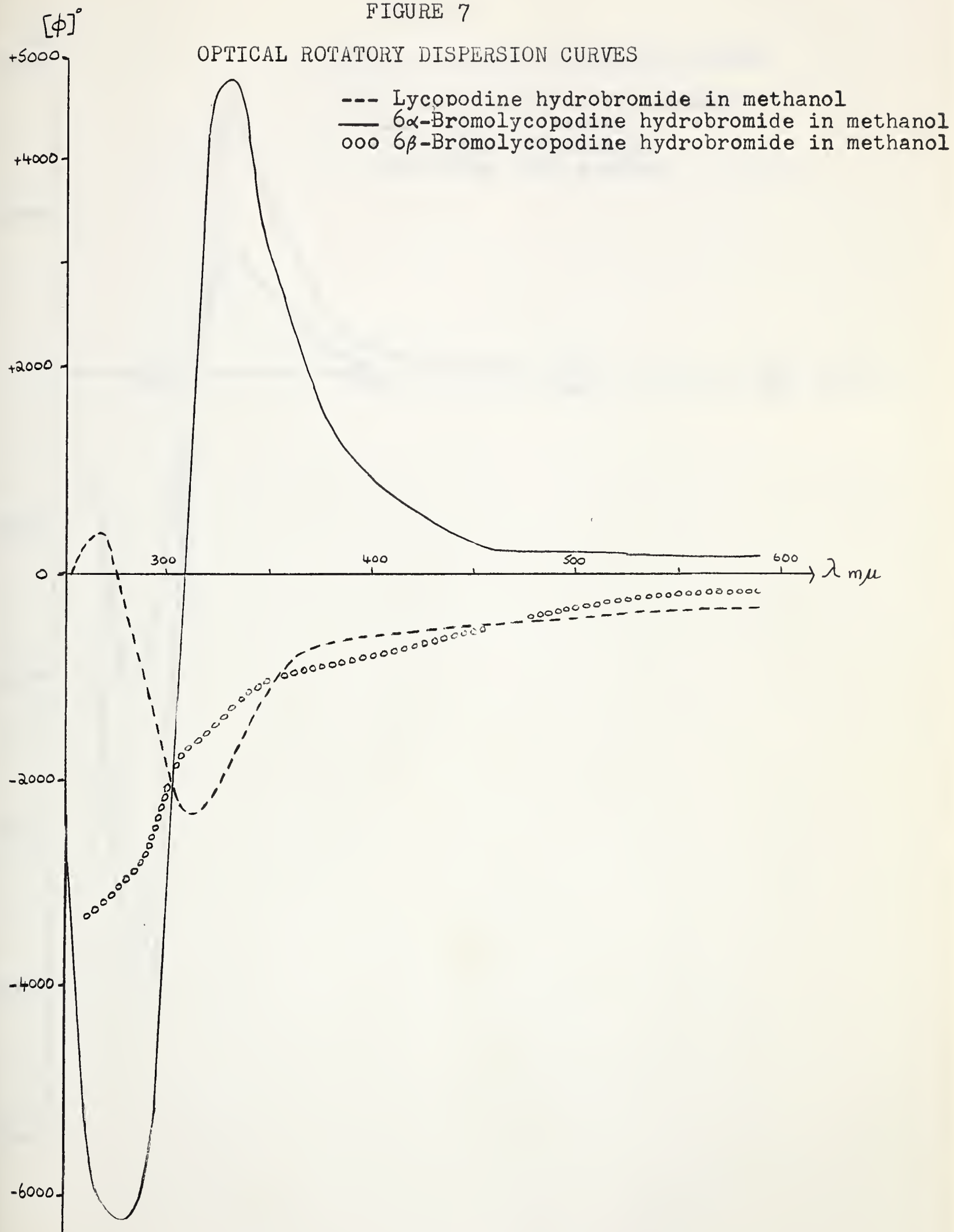






FIGURE 8

OPTICAL ROTATORY DISPERSION CURVES

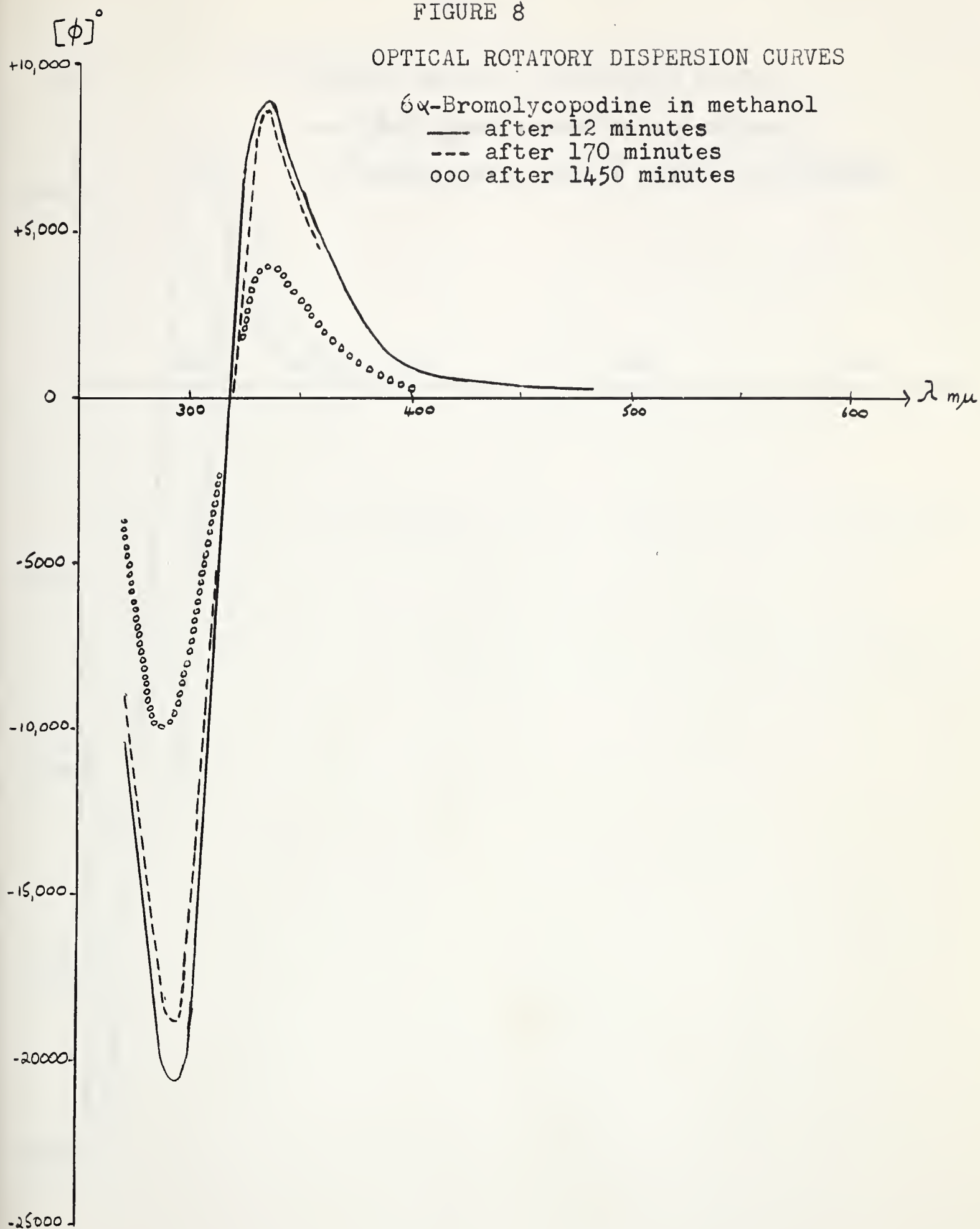




FIGURE 9

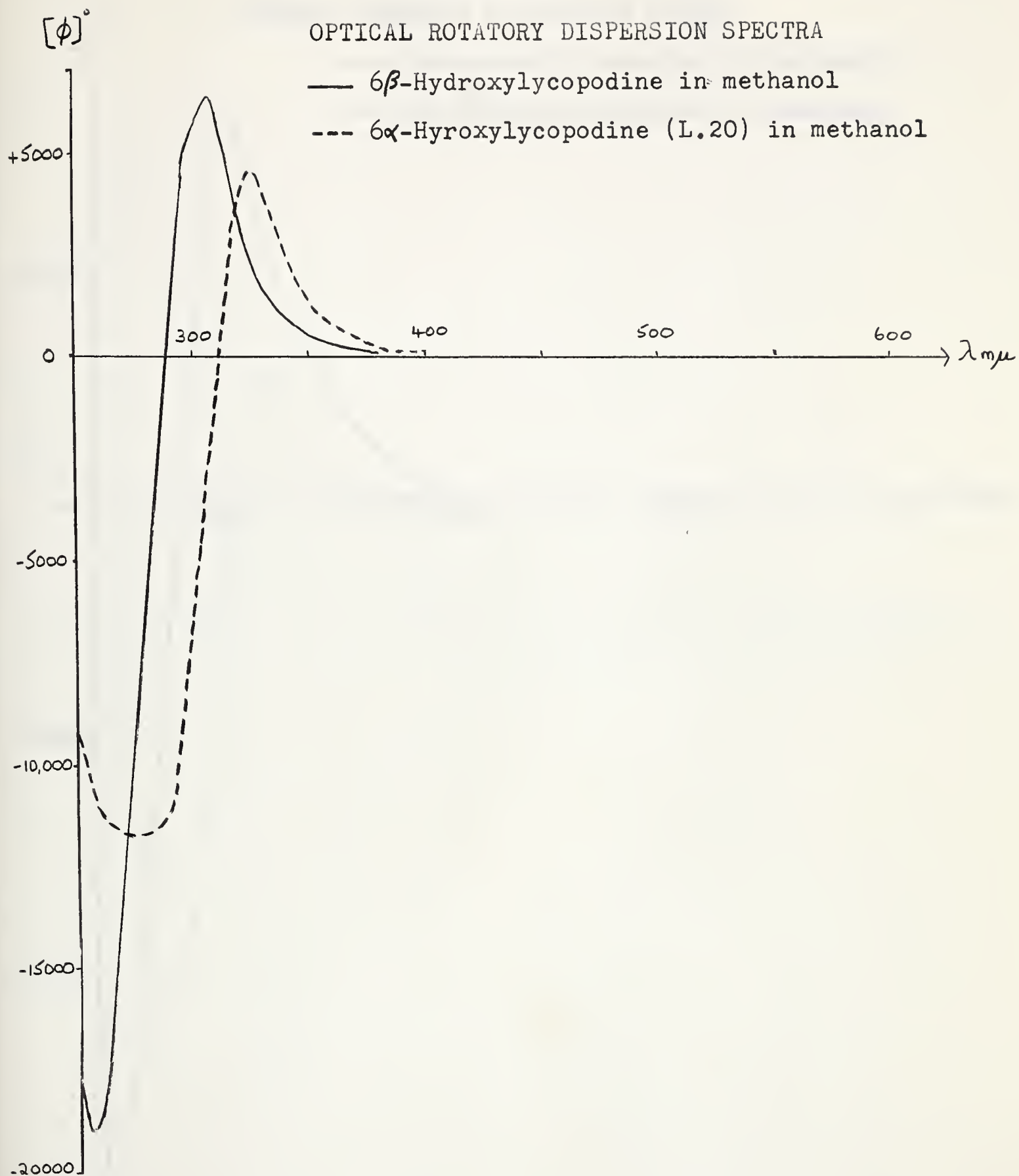






FIGURE 10

OPTICAL ROTATORY DISPERSION CURVES

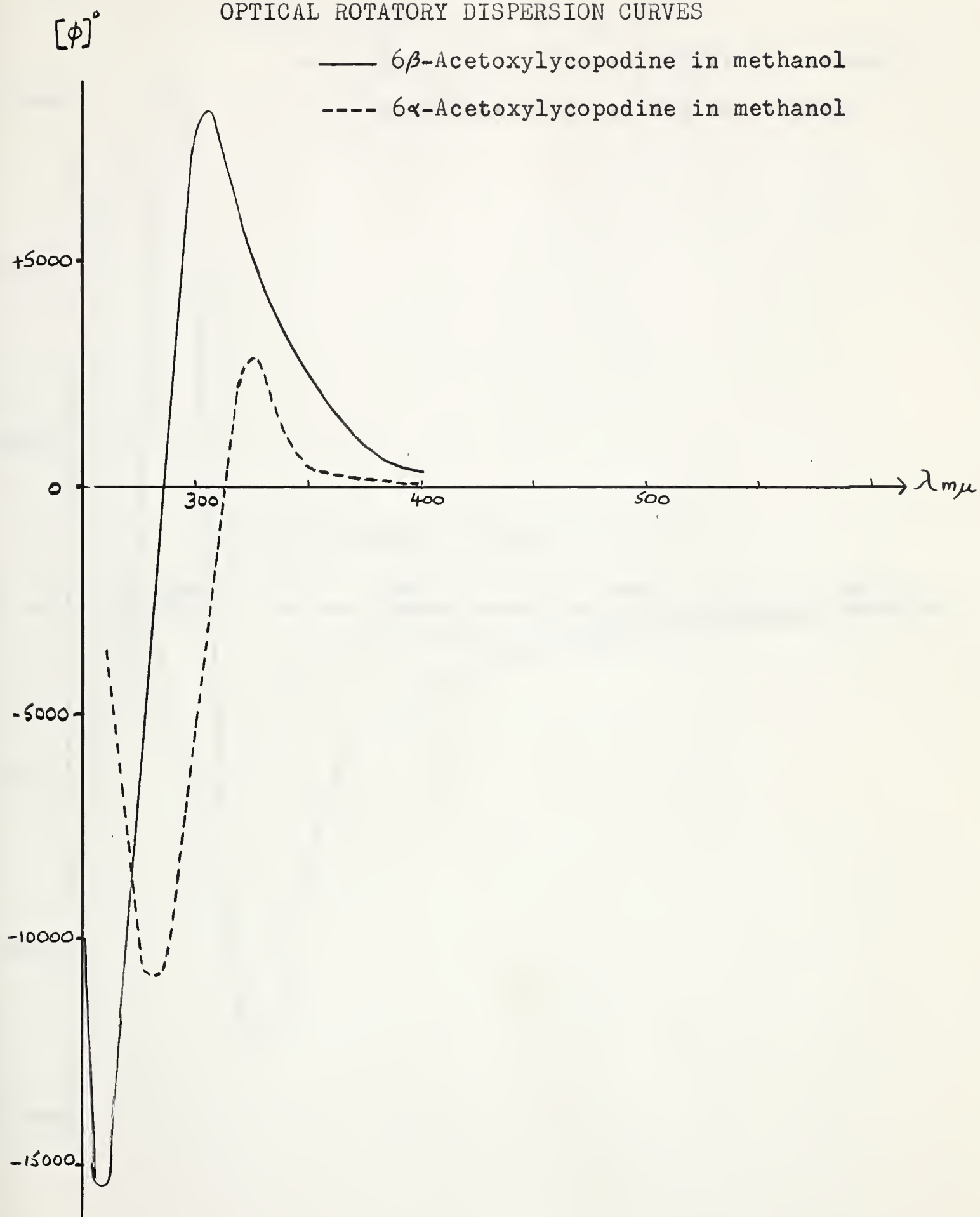
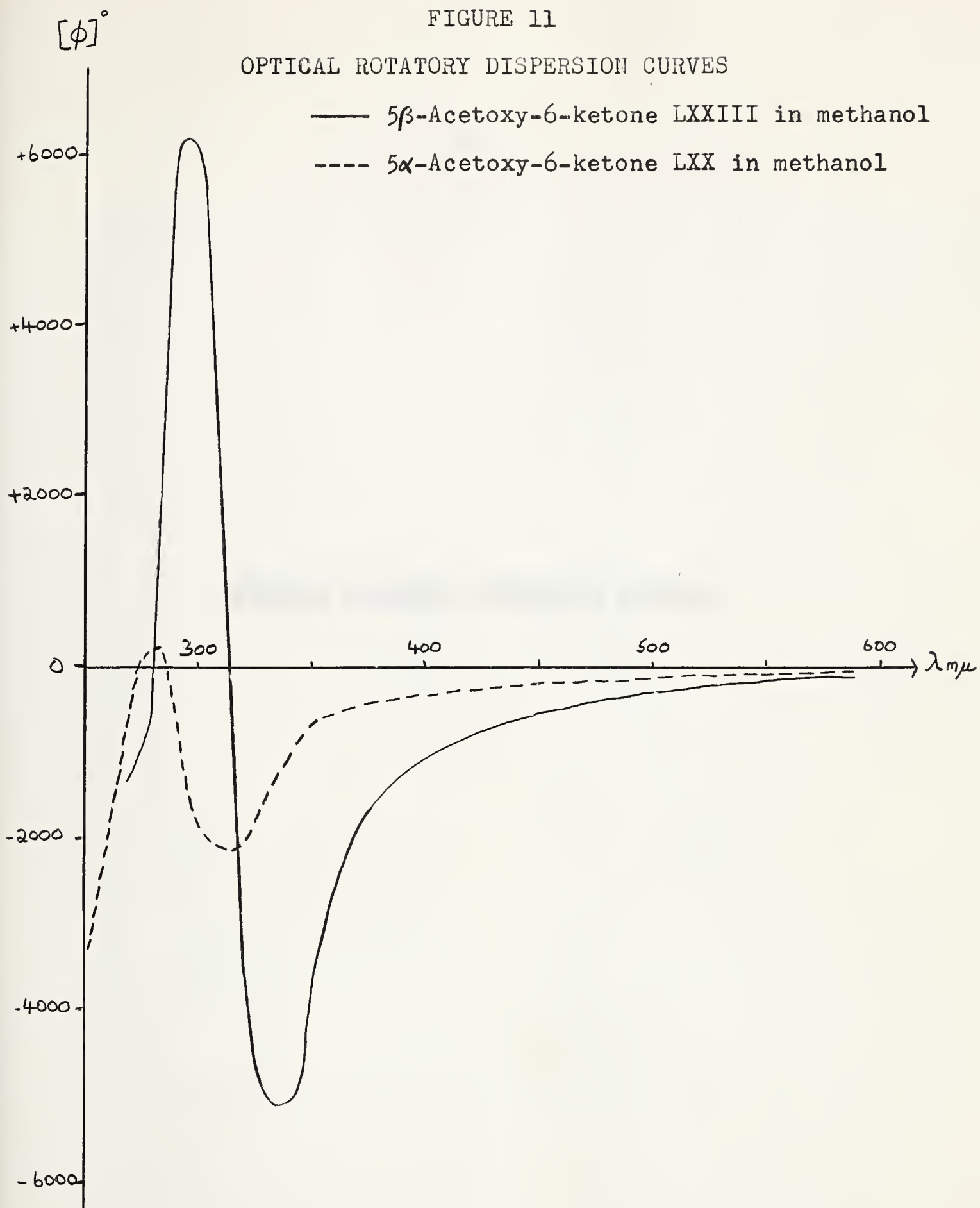




FIGURE 11

OPTICAL ROTATORY DISPERSION CURVES







NUCLEAR MAGNETIC RESONANCE SPECTRA



FIGURE 12

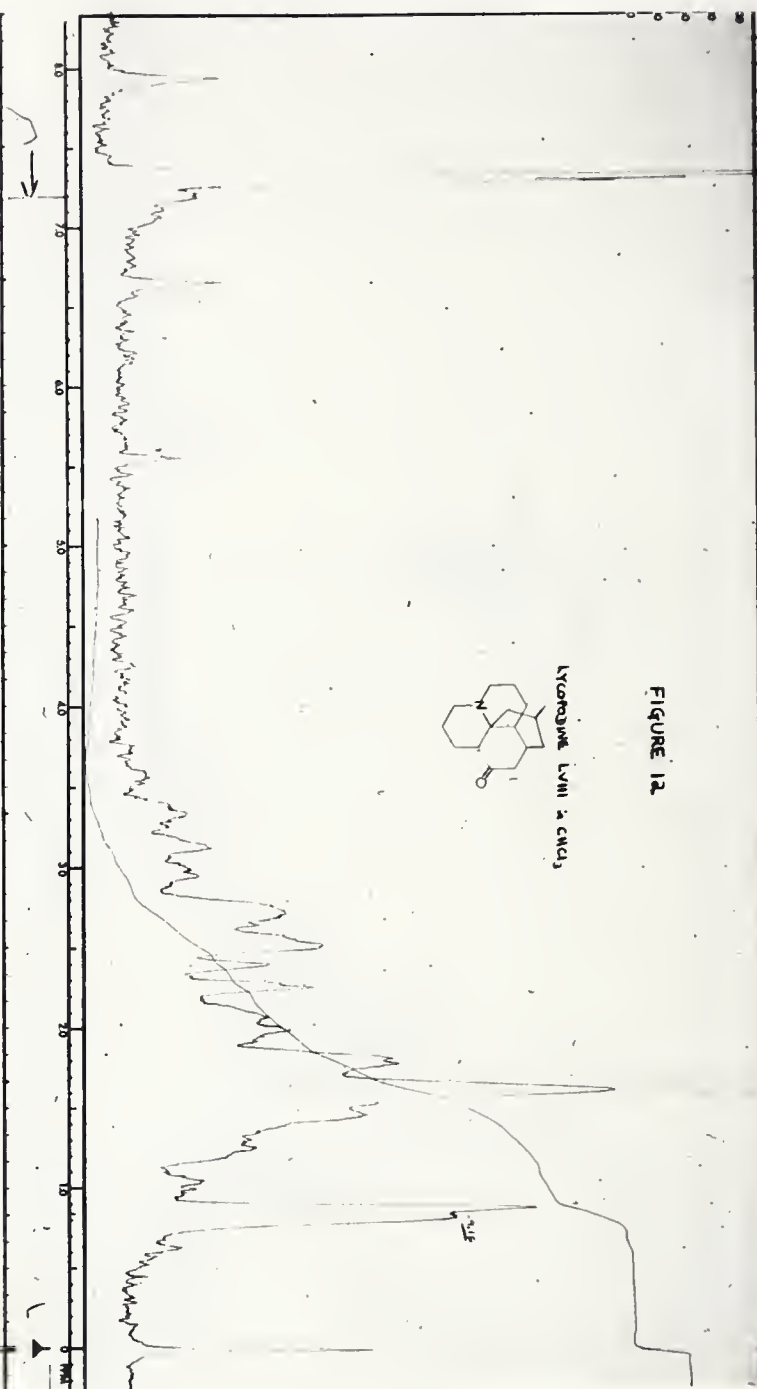
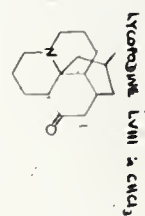


FIGURE 13

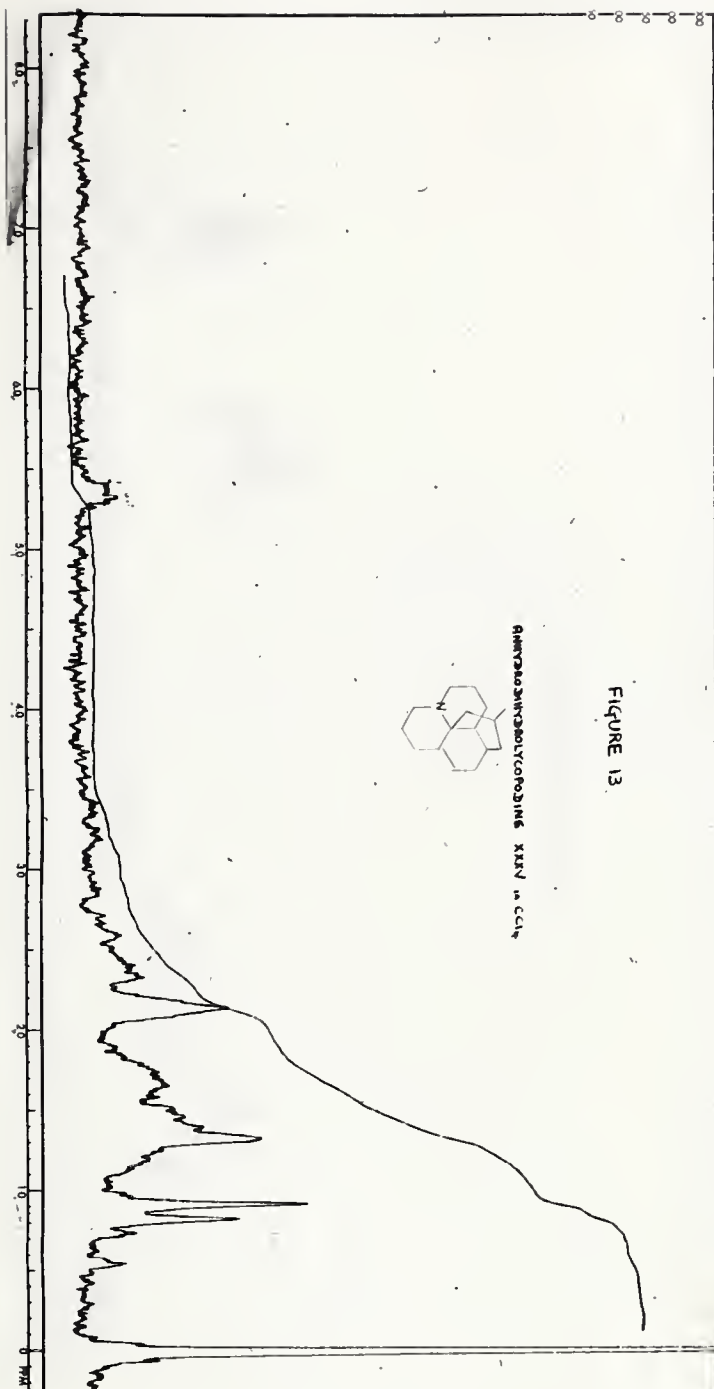






FIGURE 14

THE LINAL LAMINIS KKKII IN CCL<sub>4</sub>

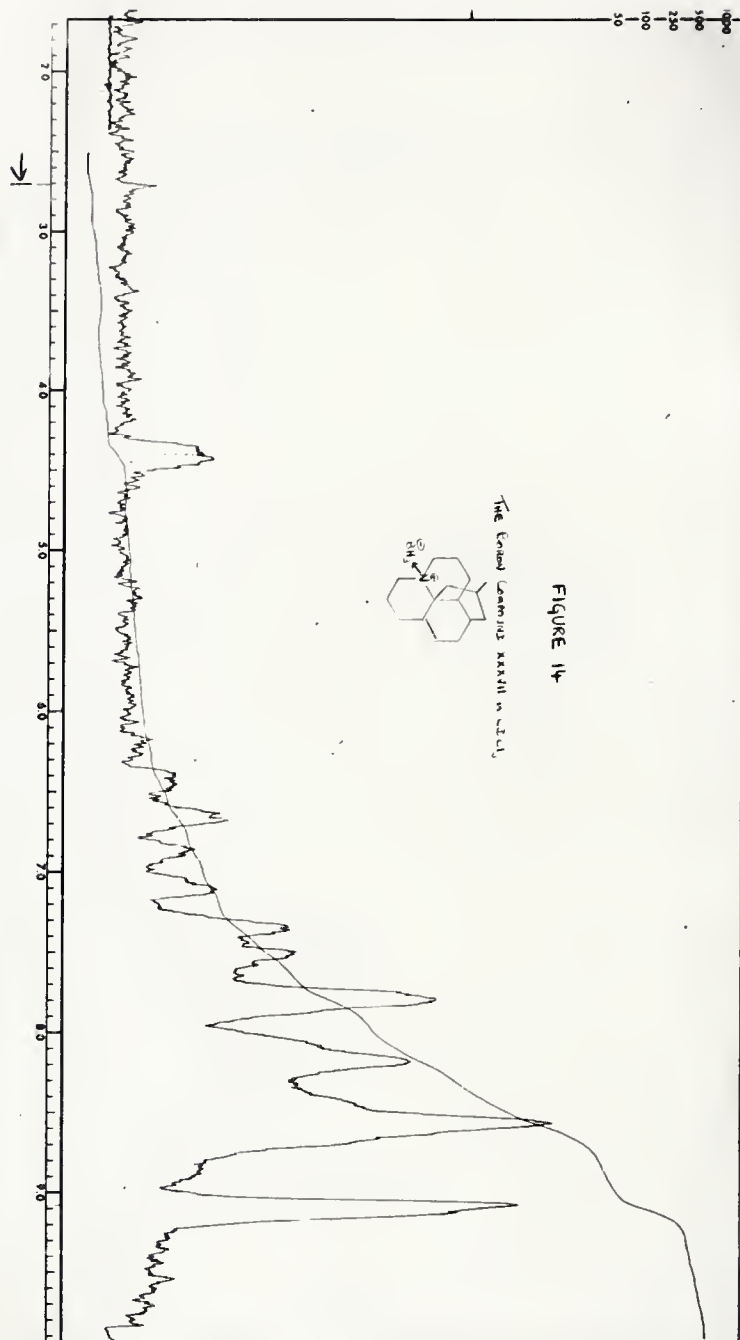
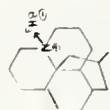
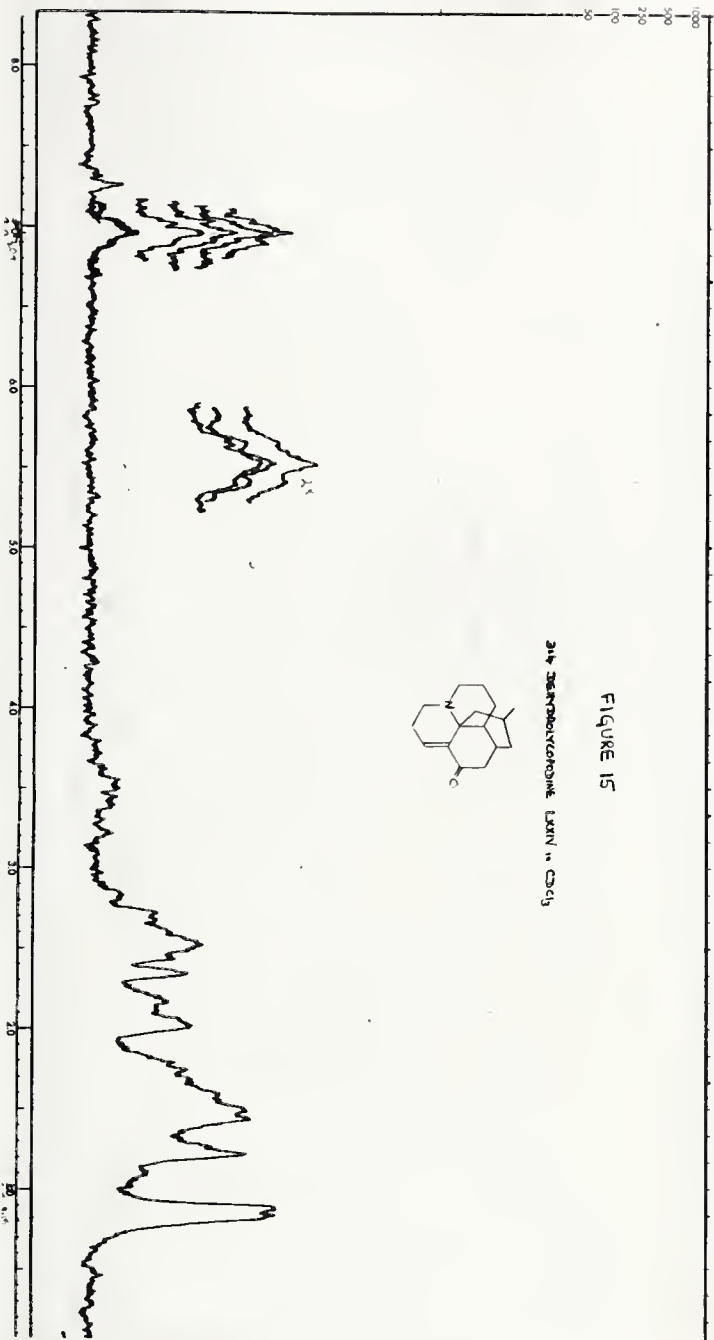
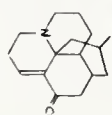
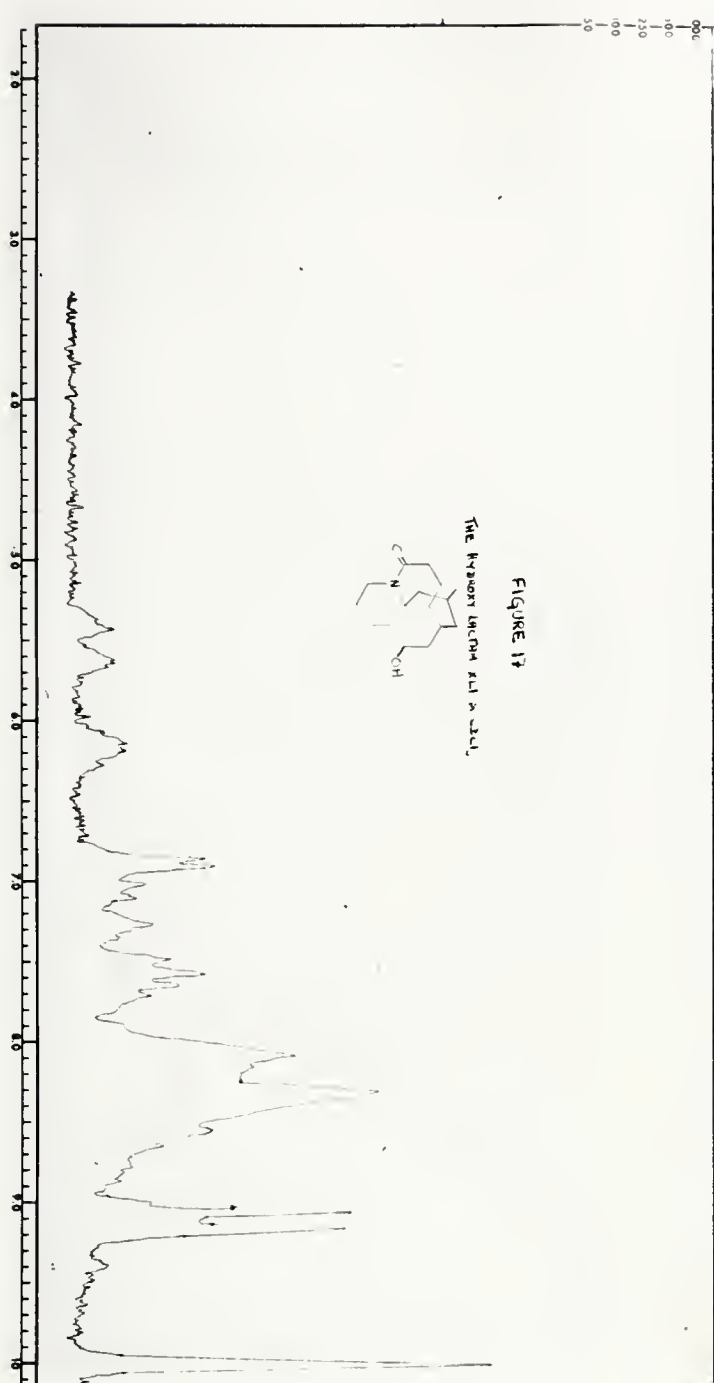
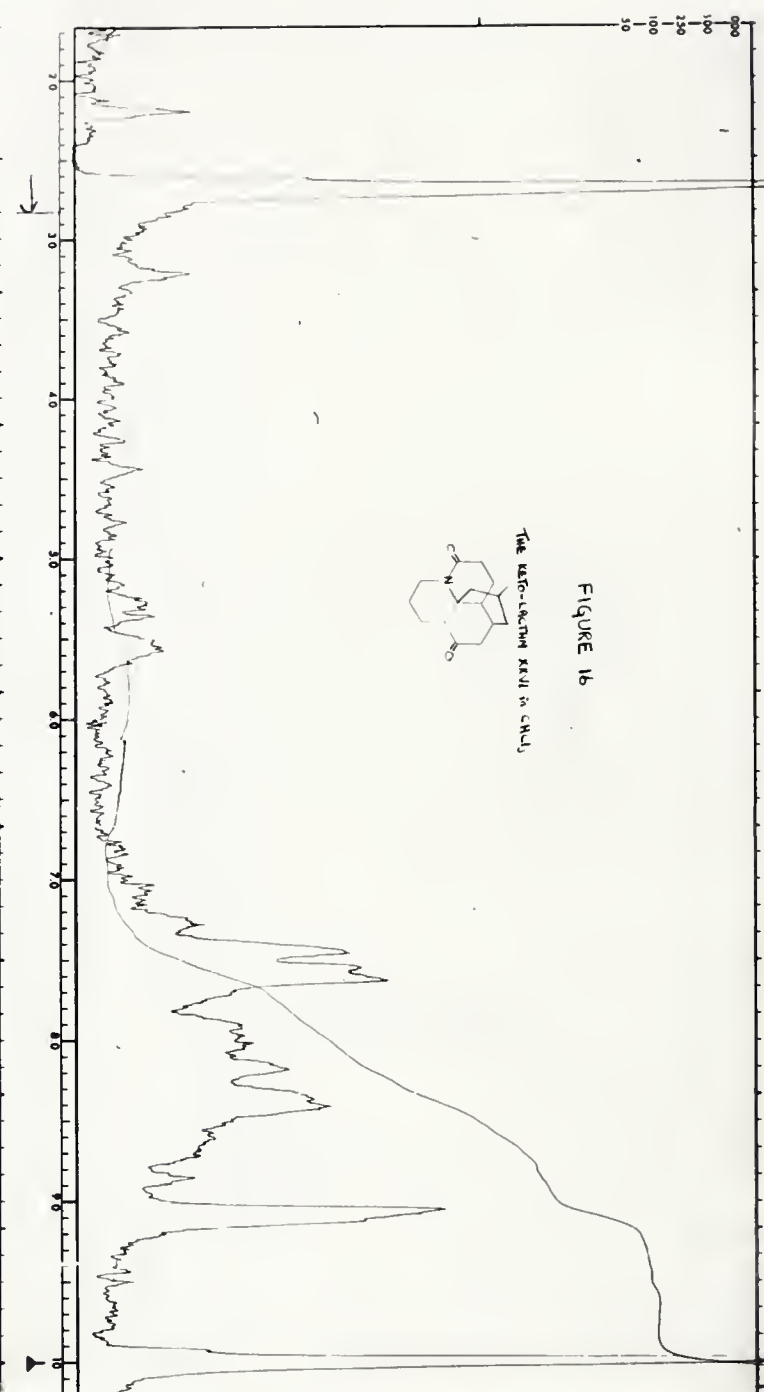


FIGURE 15

24-DEHYDROXYCORTICONE LAMIN IN CCl<sub>4</sub>











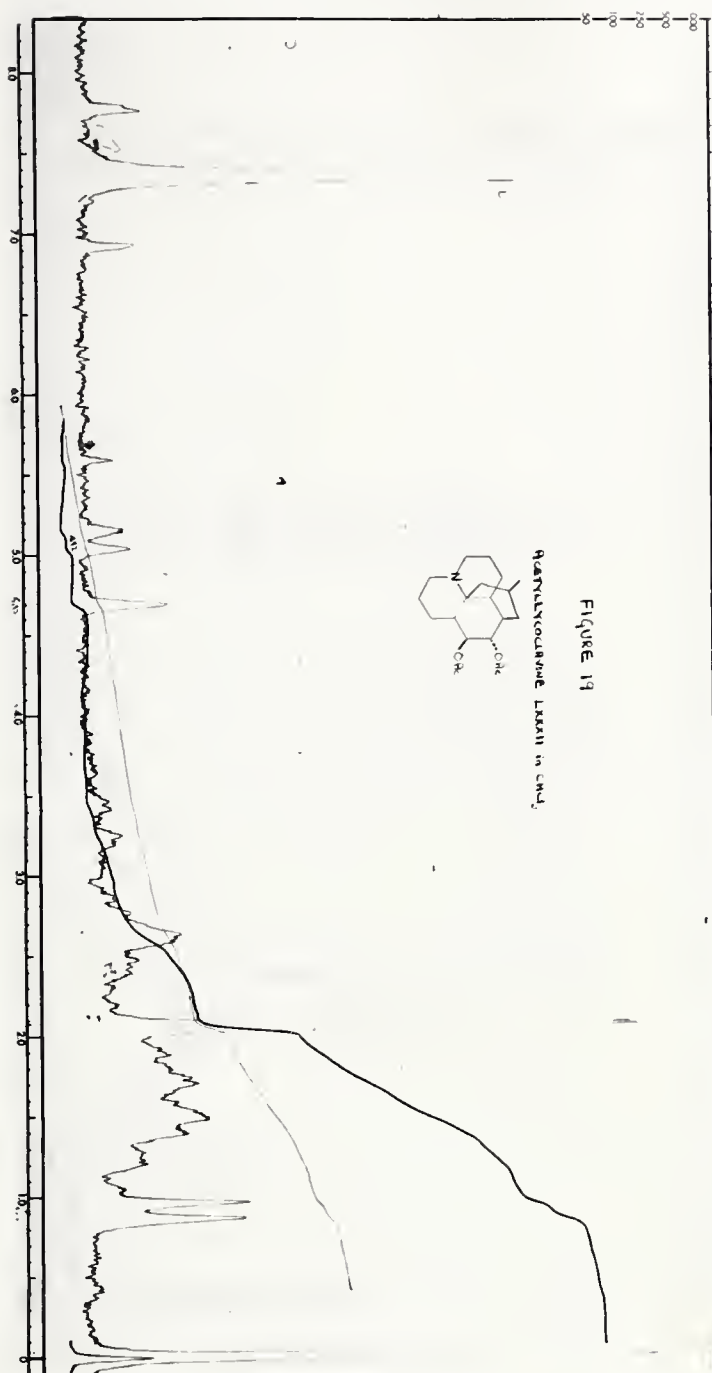
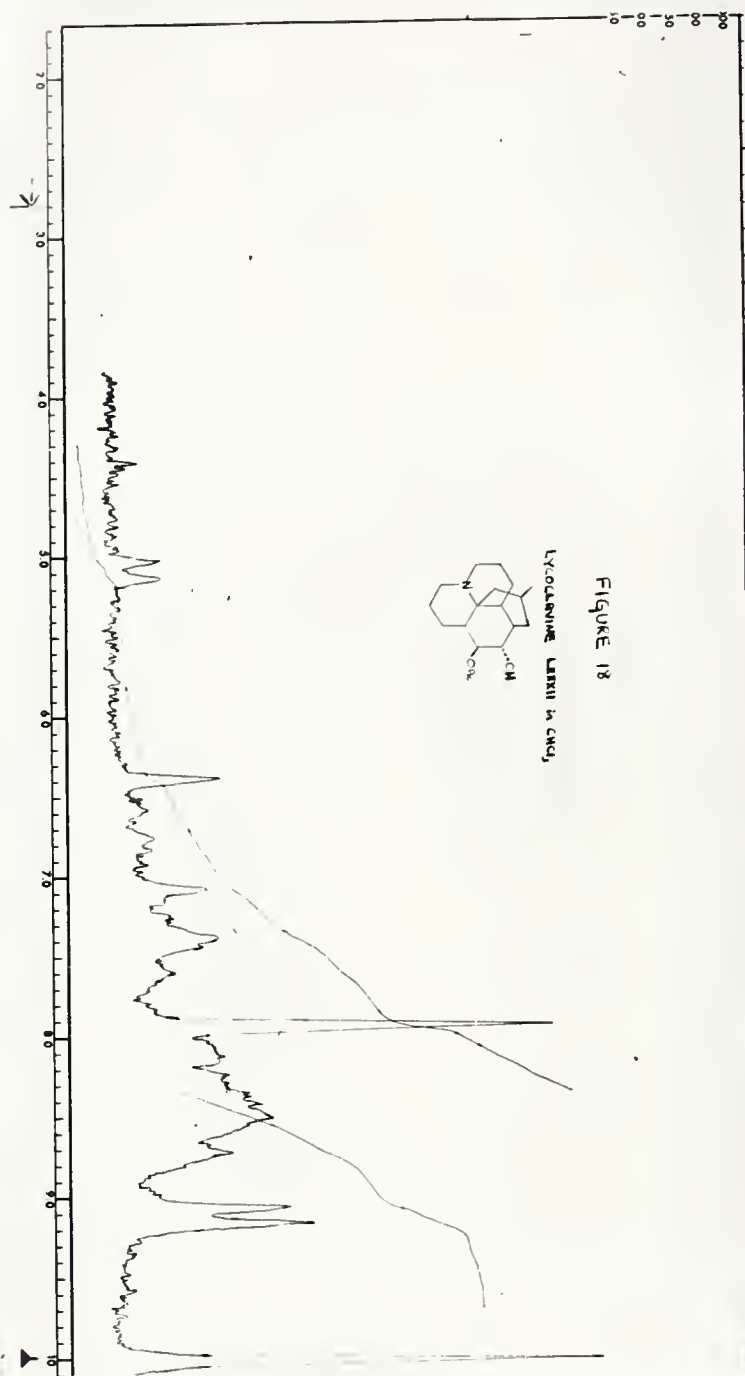




FIGURE 20

LYCOURBINONE LXIX in  $\text{CHCl}_3$

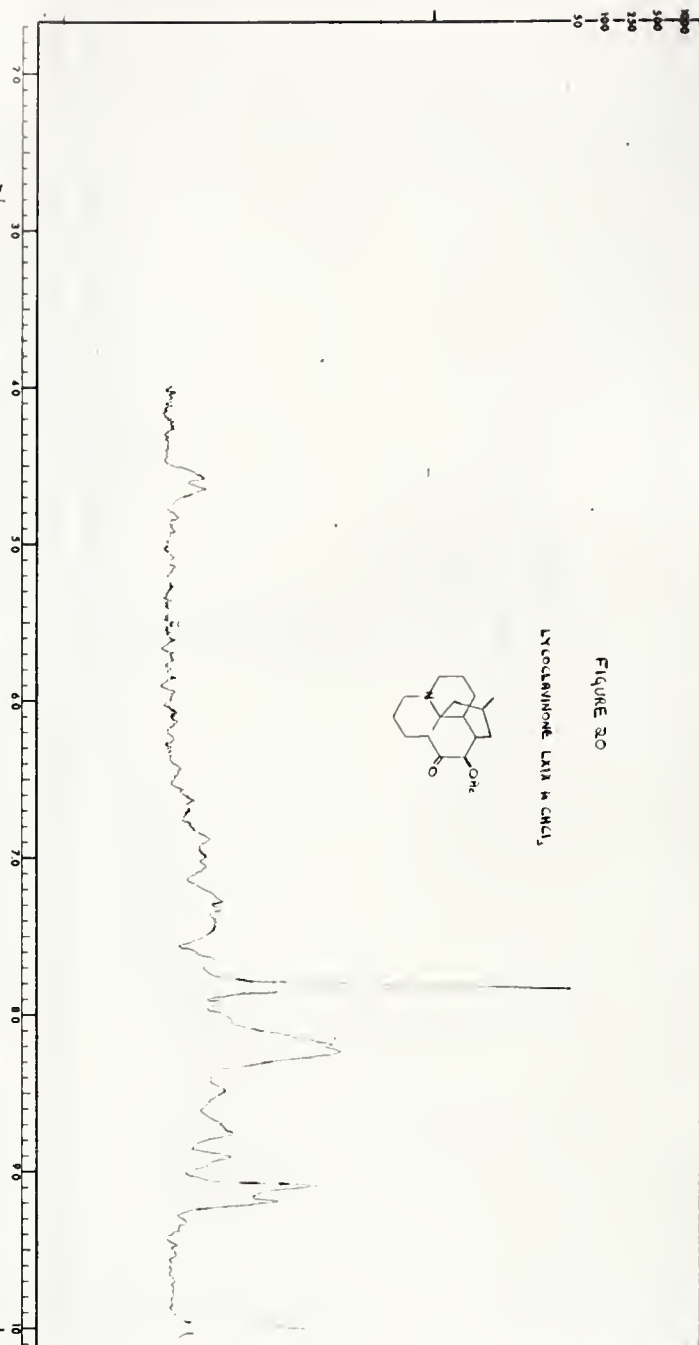
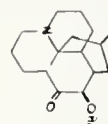


FIGURE 21

O-METHYL L-10 LXII (45%) in  $\text{CHCl}_3$

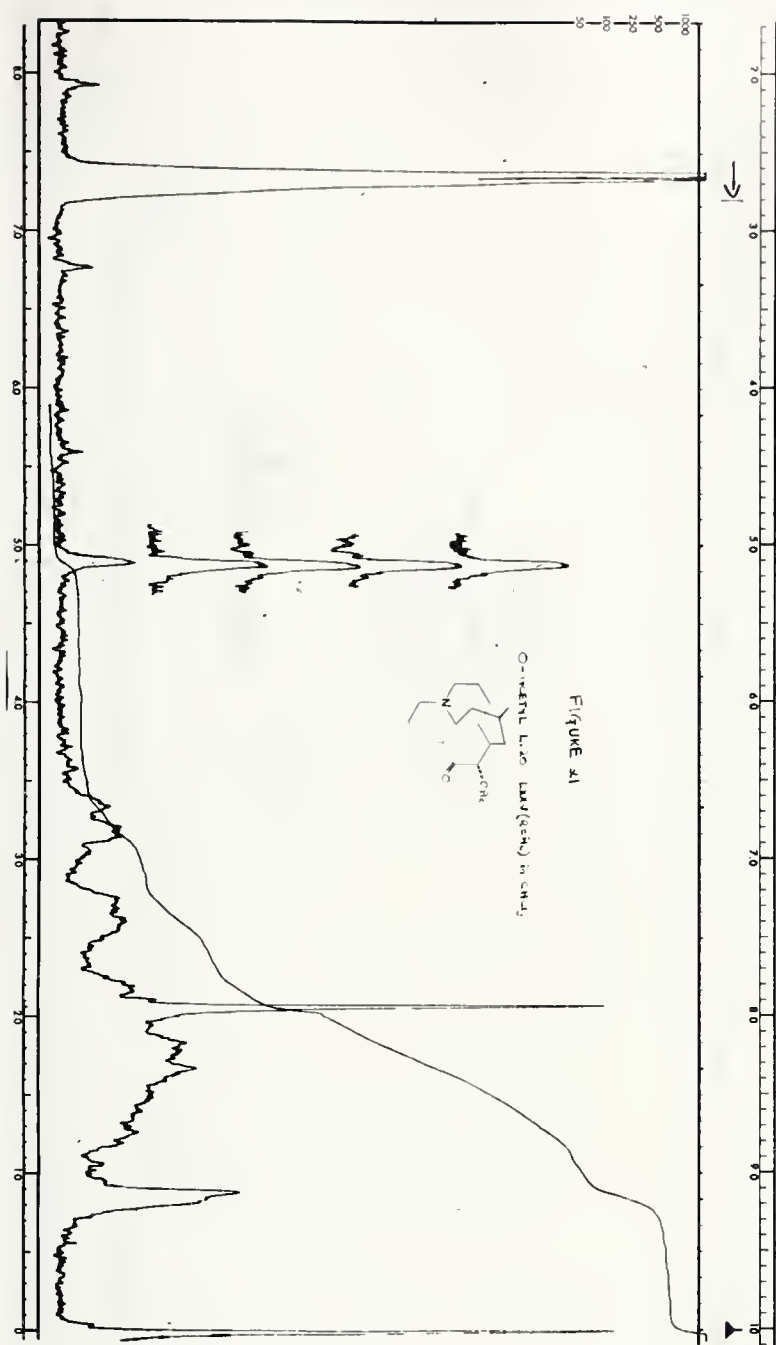
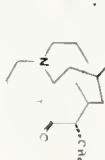






FIGURE 22

THE 5 $\alpha$ -METHYLO-6-KETONE LAMIN (K<sub>2</sub>H<sub>2</sub>) IN CHCl<sub>3</sub>

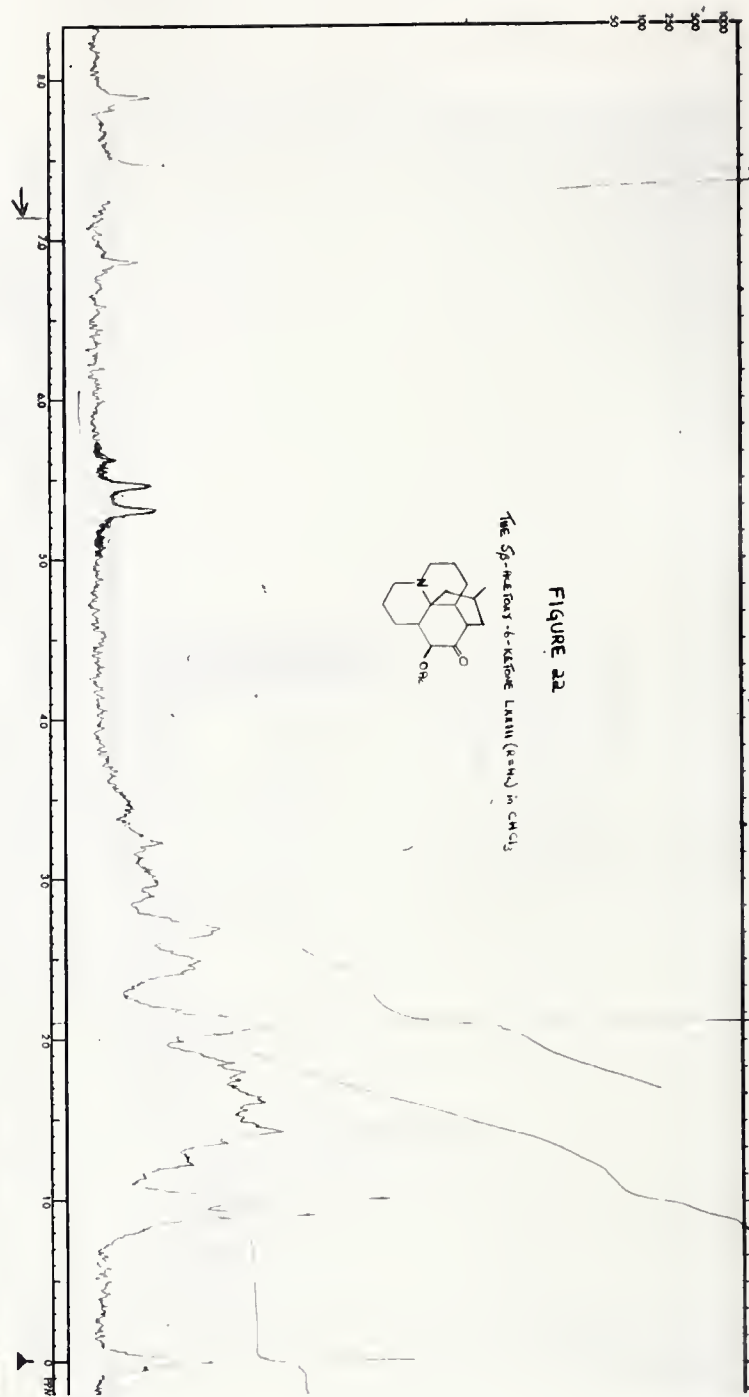
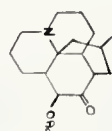


FIGURE 23

THE 5 $\alpha$ -METHYLO-6-KETONE LAM (K<sub>2</sub>H<sub>2</sub>) IN CHCl<sub>3</sub>

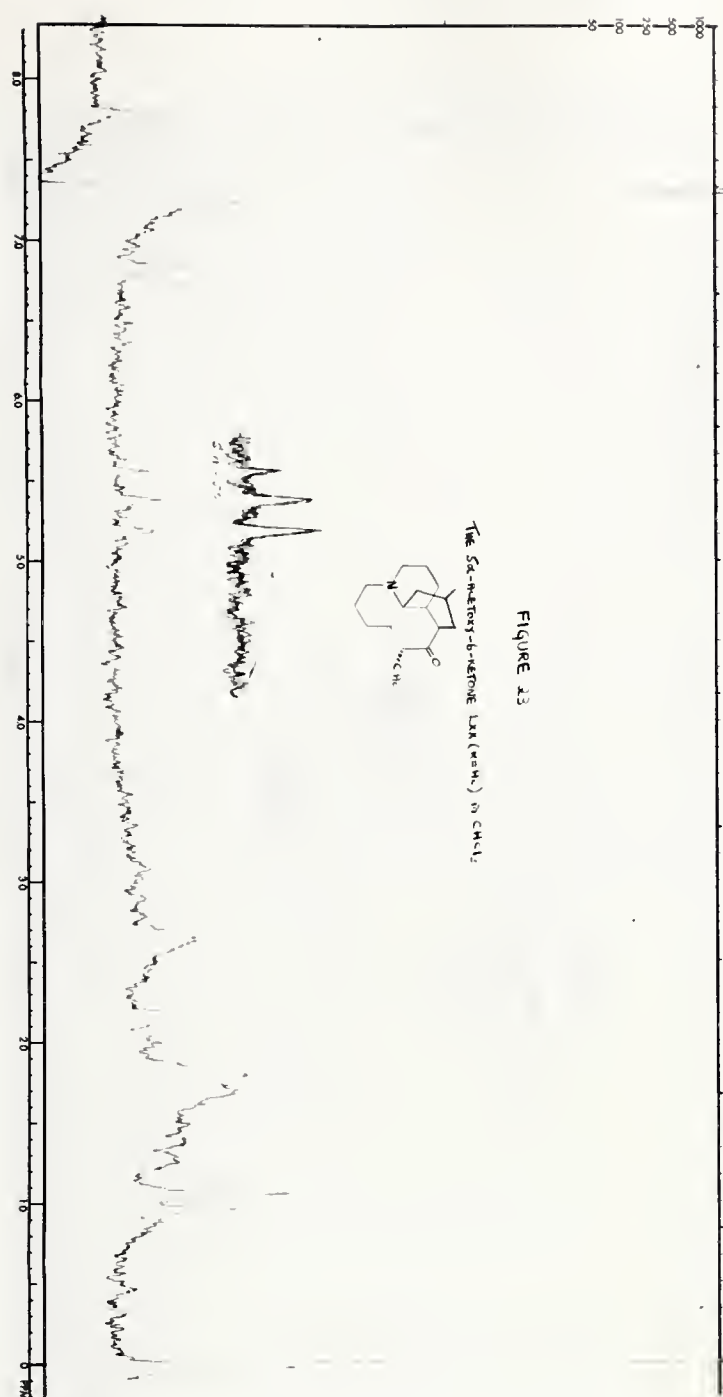
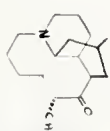




FIGURE 24

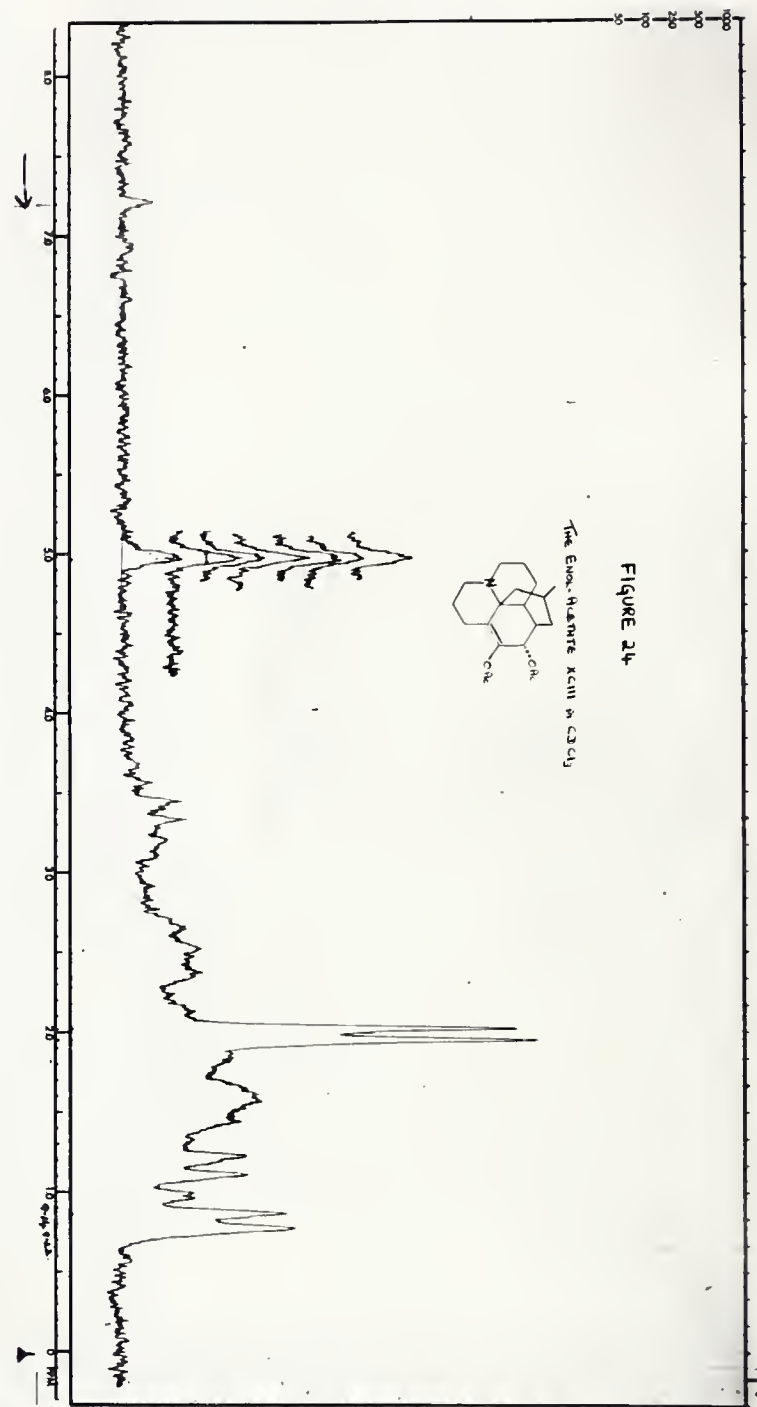
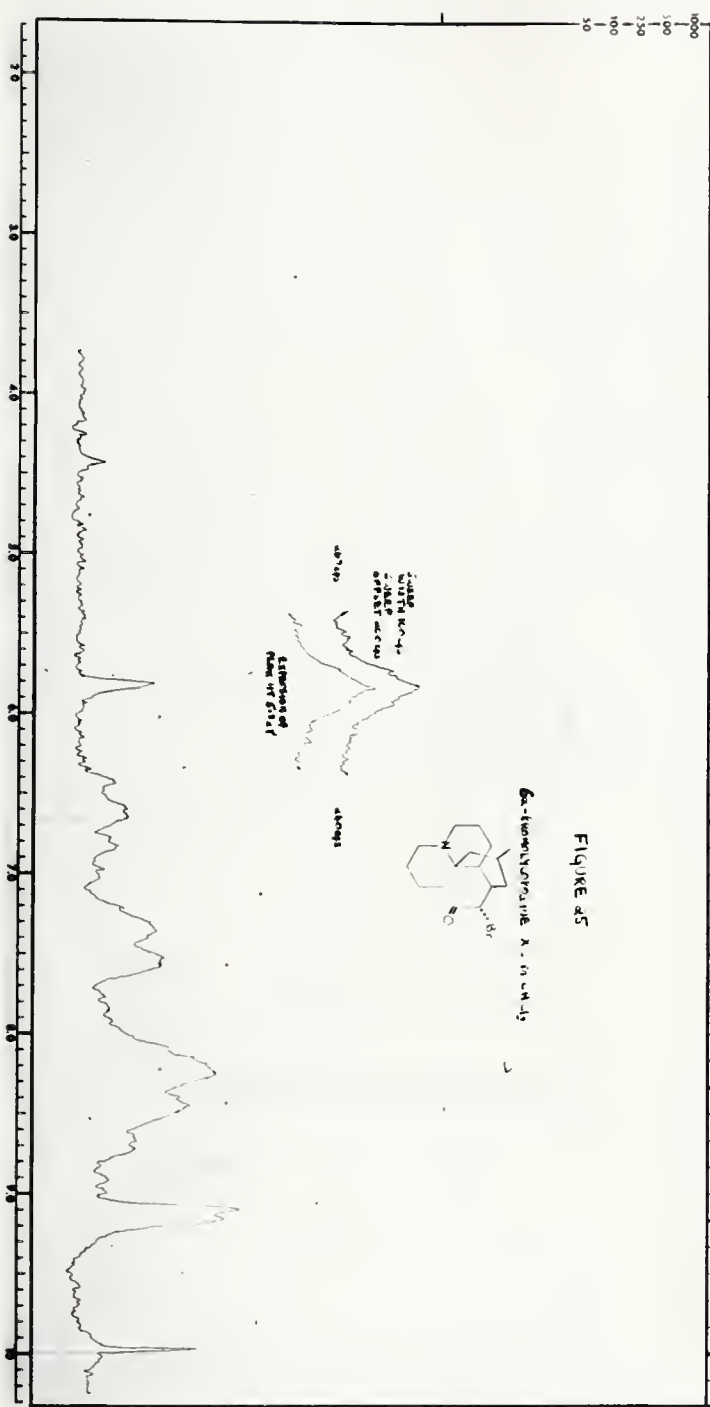
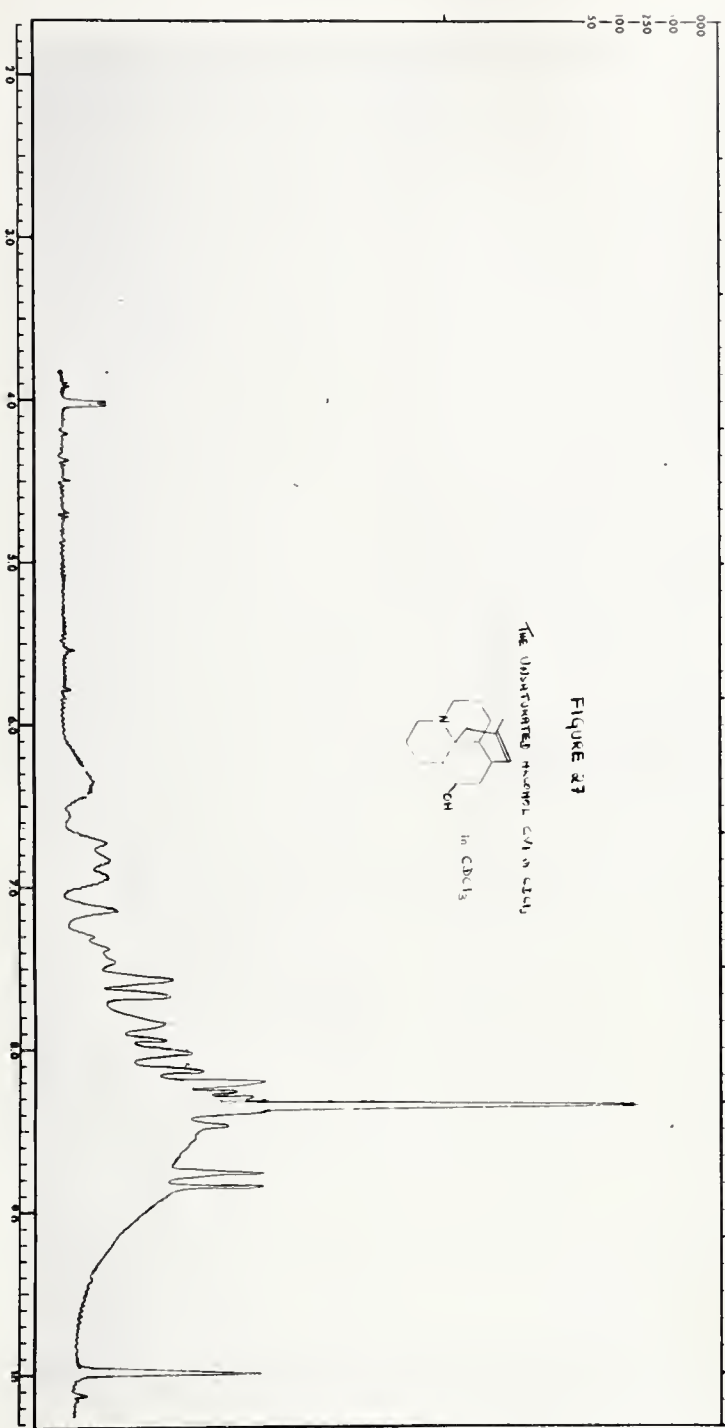
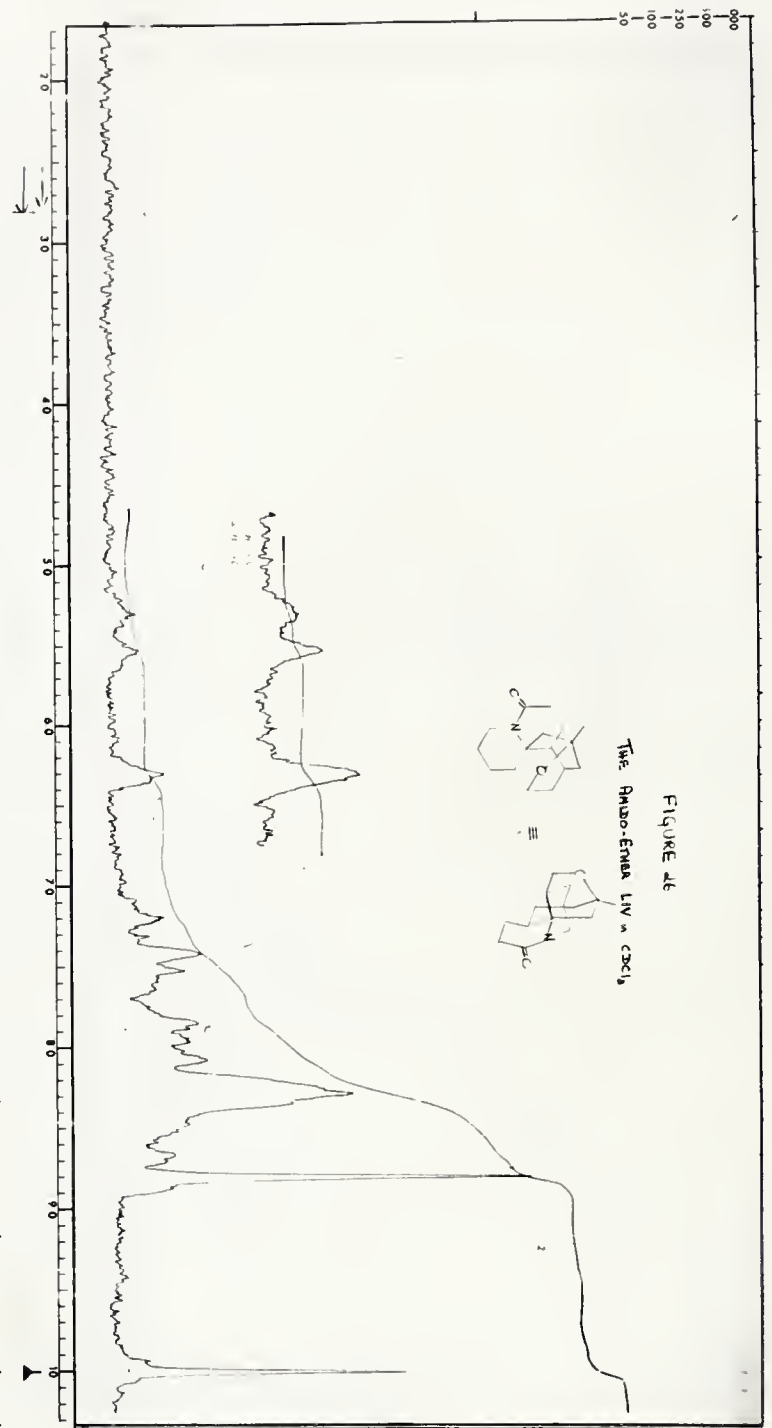


FIGURE 25

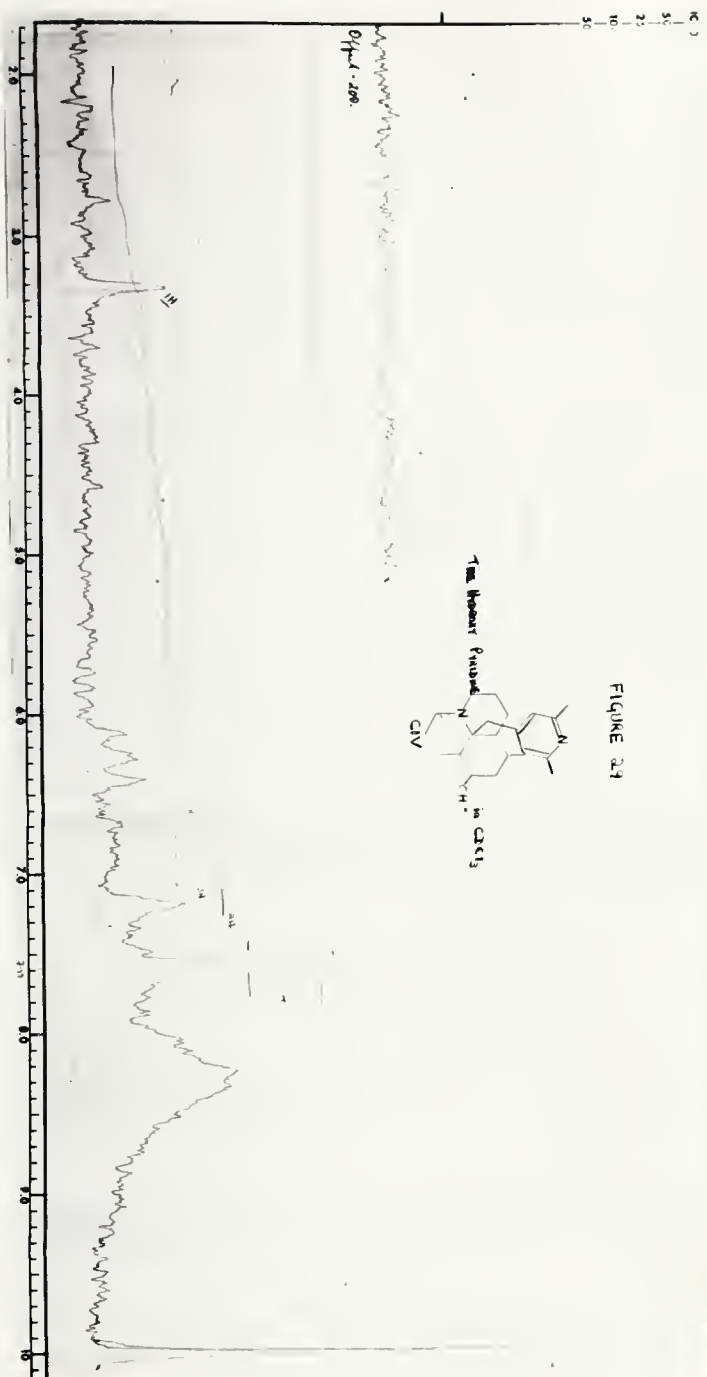
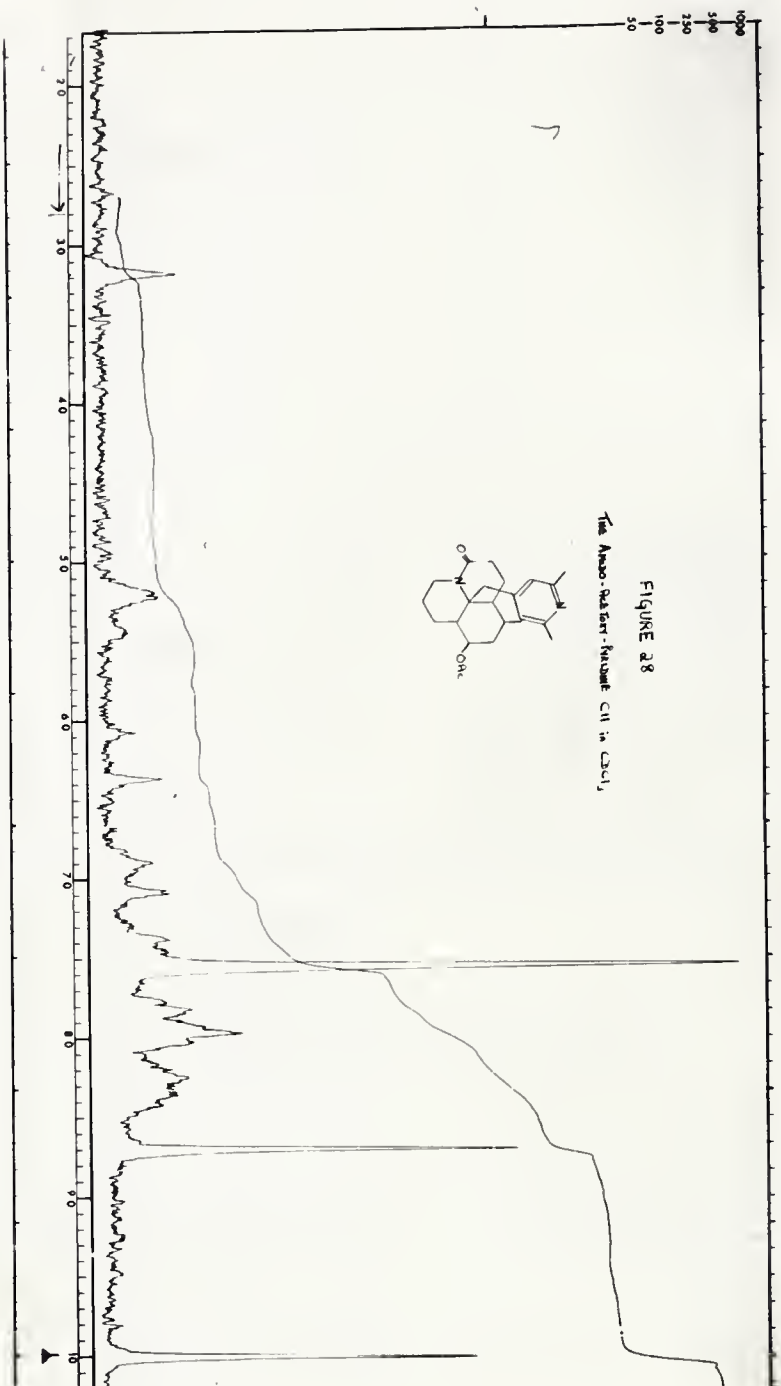






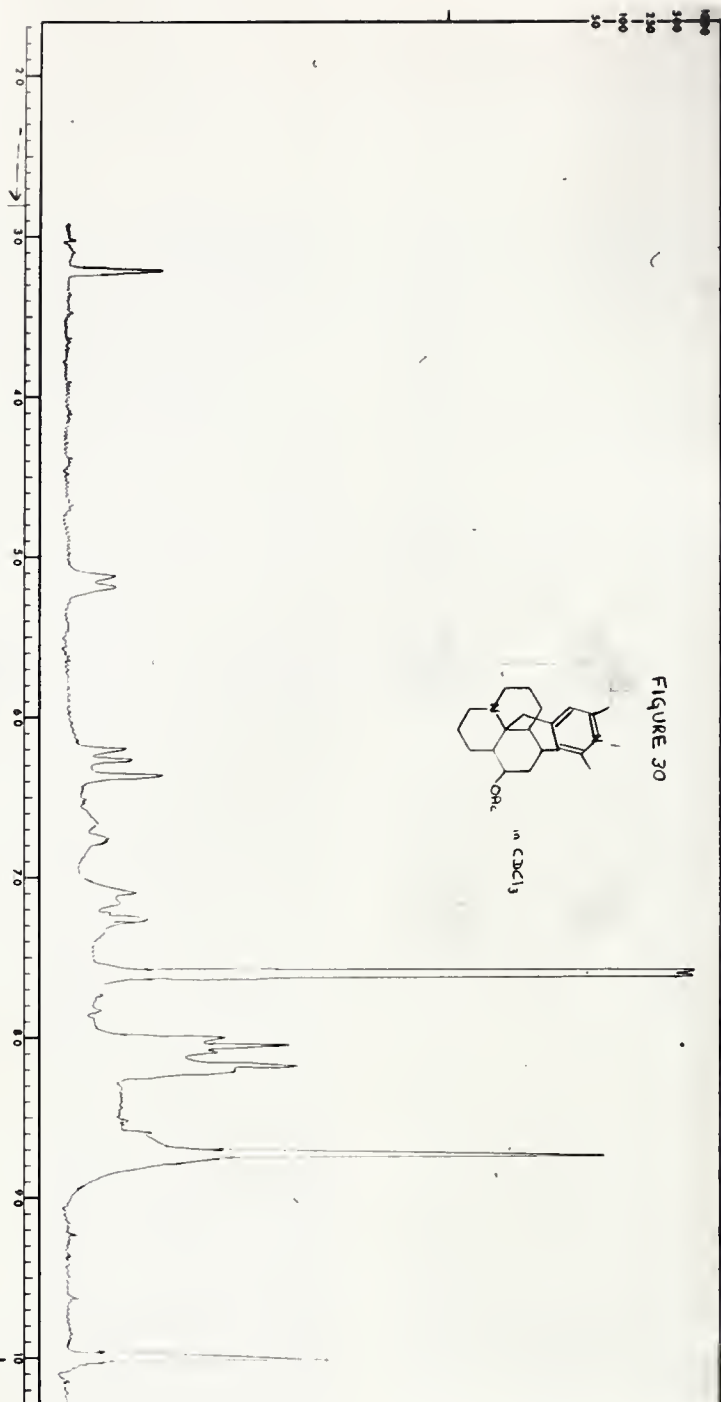
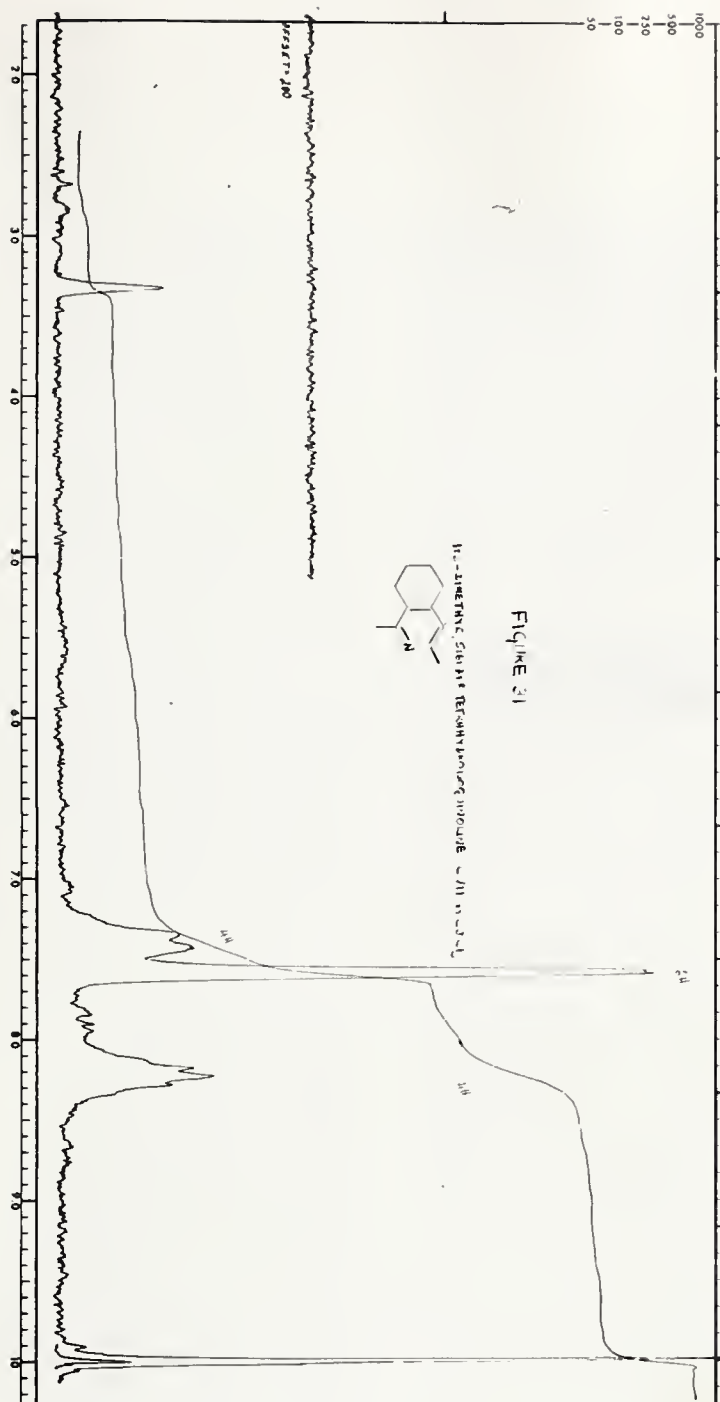














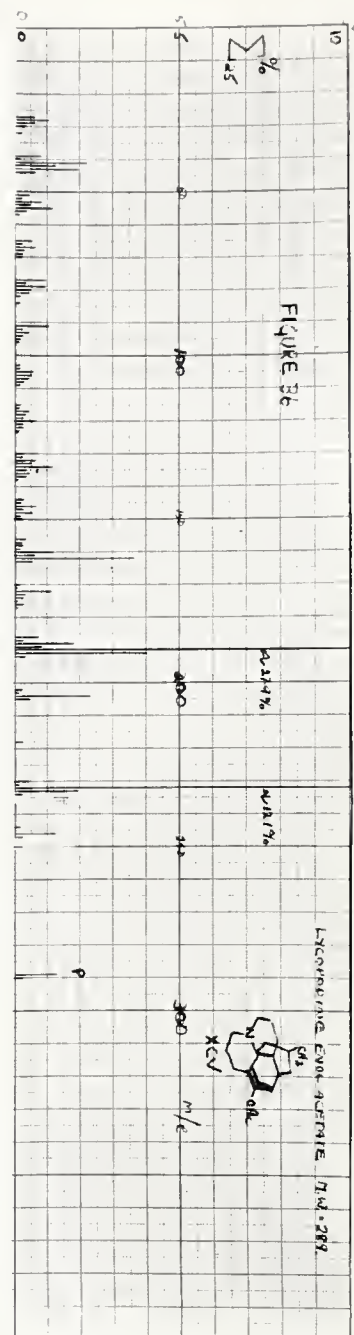
MASS SPECTRA





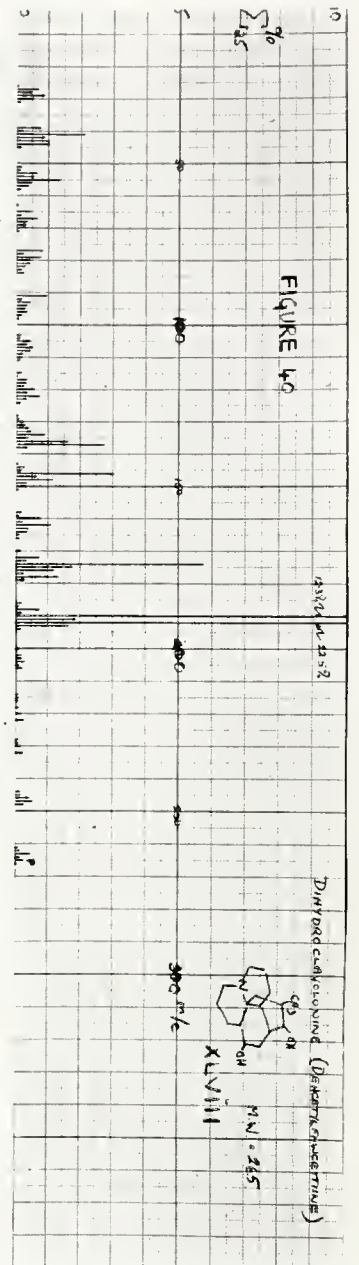




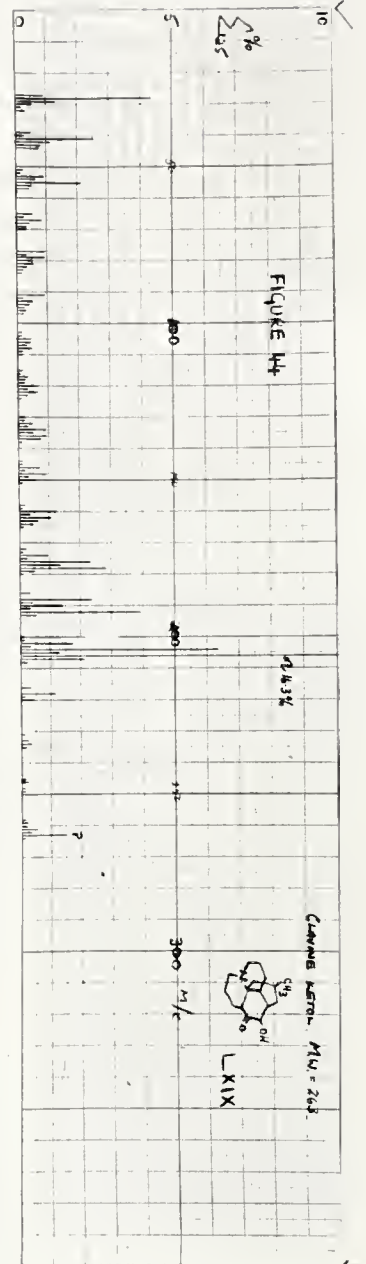






















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